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TAGE KEMP
President of the Congress

MOGENS HAUGE
Secretary General

BENT HARVALD
Vice-Secretary General

PART III

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PART III

Blood Groups and Population Genetics

Blood Groups and Disease

Legal Application of Blood Groups and other Anthropological Traits

Fisher, R. A.: Acta genet. *6*, 507–509, 1956/57

Department of Genetics, University of Cambridge, Great Britain

BLOOD-GROUPS AND POPULATION GENETICS

By R. A. FISHER

There is a rather cynical view of the progress of the Natural Sciences which represents it as consisting of an ever increasing subdivision and specialization, so that those responsible at any time for making the current improvements of natural knowledge, are represented as more and more narrow specialists, knowing, as the saying goes, "more and more about less and less". I do not, for myself, believe that such a description is appropriate in any branch of science, though it appeals to journalists and is congenial enough to purely literary men. Certainly, those who have followed, with anything like the interest it deserves, the succession of discoveries of the last few years, say since 1940, in the field of the human blood-groups, might be tempted to make a diametrically opposite generalization, and to declare that whenever genuine progress, in the great sense, is achieved, fields of study hitherto disparate and unconnected, are suddenly seen to be inseparably linked, and to fall into place as aspects, distinguishable only by differences of training and technique, of a single grand science, or field of study.

At the present time, indeed, the Sciences of Demography and Vital Statistics, of classical Human Biometry, and of traditional Ethnography in its physical aspects are pursued as if they were independent disciplines. They are, none the less, irresistibly destined to be merged in a Science so far nameless under the catalystic action of the new knowledge of the blood-groups, together with a few other cognate factors, the "Honorary Blood Groups", such as the *secretion* factor, that responsible for taste discrimination of *phenylthiocarbamide*, and the common anomalies of colour vision known as *Daltonism*.

The potency of this new agency derives from several sources. The human species excels all others in the abundance of individuals exposed

to study. Biometry and demography have in different ways exploited this abundance. The human individual, moreover, exposes himself readily to expert examination, especially when under medical care. Moreover, his species is in a third respect uniquely suitable for the pursuit of population genetics, in that it is his traditional practice to keep his own pedigrees, with, on the whole, a very commendable accuracy. Population genetics, which was, as it were, born out of biometry under the influence of the theoretical understanding due to Mendelism, finds therefore its ideal field of study in the human species. It is, however, the existence of recognizable single factors, to all appearance selectively stabilized, though evidently capable of slow changes in frequency under the selective influences of climate, disease and social organization, which make it reasonable to hope that we shall in this species be able to confirm and correct our theoretical ideas by quantitative observational data. In all species manifest polymorphisms offer attractive opportunities for penetrating the complexities of the genetical situation; the abundant polymorphisms of the human race should encourage us to a far more detailed analysis than would otherwise be possible.

The comparative ease with which certain aspects of population analysis are made possible by blood-group studies, have already revealed ethnographic distinctions with a detailed precision quite unattainable without their aid. Although inevitably some ethnographers have at first felt ill at ease with the new facts, and what is indeed much more important with the new *potentialities* of serological studies, yet from a wider point of view it must be evident that all that ethnography strives to do will be facilitated beyond precedent as our knowledge of the blood-groups is extended. The traces left on existing populations by such past events as race mixture, by the relative expansion or attentuation of numbers, or by evolutionary modification under environmental influences, have certainly not by existing means been successfully unravelled. In considering the use of blood-group evidence in clarifying the ethnic history of Man, the peculiar advantage should be emphasized that independent evidence is within reach from different parts of the human germ plasm, so that independent confirmation should often be obtainable from the evidence of different factors independently inherited.

Although surveys on a national scale with a limited range of reagents have suggested themselves as the first requirement in exploratory work, many recent discoveries have emphasized two facts which might not have been anticipated. One is that certain rare genotypes such as homozygous D-- of the Rhesus system, homozygous Tj^b and Ve^b though, so far as is

known, everywhere exceedingly rare, are yet rather widely disseminated in different Continents. Hospitals in all parts of the world, therefore, may need access to the special reagents which may be required for their recognition, and in some cases, for the discovery of compatible donors. Secondly, it has been shown in several cases, as with the group known as *Diego*, that an allelomorph exceedingly rare in tolerably well studied populations of European origin, may be much more frequent in non-European races, and to supply unsuspected means of racial discrimination, through the polymorphism they determine being quantitatively important in those parts of the world. Both these facts point to the need for extensive documentation of rare reactions, and of extensive facilities both for storage and for investigation of reagents having unusual qualities.

In the course of our Sessions we shall indeed be hearing a good deal of these factors involving rare alleles. Those who have made progress in their elucidation have had to overcome great difficulties, and I hope we may also discuss what practical steps can be taken towards such international cooperation as will alleviate these difficulties, and prevent work of this kind, in its further prosecution, from becoming intolerably burdensome.

Mourant, A. E.: Acta genet. 6, 509–515, 1956/57

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ANTHROPOLOGY AND NATURAL SELECTION OF BLOOD GROUPS

By A. E. MOURANT

In 1910 Professor and Mrs. *Hirzfeld* showed that there were wide differences in the frequencies of the ABO blood groups between the populations of many of the chief countries of the world, including those of Europe. When *Boyd* made his great compilation in 1939 it was becoming clear that the peoples of many of the individual countries themselves were

significantly heterogeneous with respect to the frequencies of the A, B and O genes. The rather scanty data then existing for the genes of the MN system seemed to show much less heterogeneity, even over large areas such as the whole of Europe.

Up to this time and for several years afterwards it was generally assumed that natural selection in relation to the blood groups was negligible. The highly characteristic ABO frequencies of various populations were therefore treated as though they had existed almost unchanged for thousands of years, and were made the basis for elaborate classifications and speculations.

If natural selection was negligible, some other origin had to be found for the wide differences in ABO frequencies. The most favoured was based on 'genetic drift': it was assumed that while man was still a rare creature living under unfavourable conditions some thousands of years ago, small groups suffered wide random fluctuations in gene frequency, and in some cases the accidental loss of one or two genes. When conditions, especially climate, improved, numbers increased rapidly and the existing accidental gene frequencies became stabilized.

At present considerable bodies of data exist for the distribution of the genes of most of the blood group systems but only in the case of the ABO, MN and Rh systems are they adequate to allow us to see whether important local fluctuations are superimposed on the major regional variations. Data for the ABO system are, however, so very much more abundant than for the other systems that there is a danger of exaggerating the importance of local variations in ABO frequencies which might have been missed in a less detailed survey.

From the point of view of blood groups we can classify the peoples of the world into about eight divisions each occupying a continent or a major portion of a continent. Each of these is characterized by a particular average set of frequencies of ABO, of MN and of Rh blood groups, usually differing considerably from those of all the other divisions.

The next convenient level of sub-division is, in most cases, that of the national units. In Europe there are wide variations in ABO frequency from one country to another. In the whole of Europe west of the Baltic Sea and the River Elbe, and north of the Alps and Pyrenees (but omitting the Basques and the Lapps), the variations in frequency of the Rh and MN groups are very small. The uniformity extends in this case to the many phenotypes of the Rh and MNSs systems. In tropical Africa the variations in Rh and MN frequencies are somewhat greater than in northern and central Europe but are less than those affecting the ABO groups.

Among the aboriginal peoples of America, the variations in Rh and MN frequencies are small but those affecting the ABO groups are very great: the Eskimos have all three genes A, B and O, the Indians of Canada and the United States have A and O with a very wide range of frequencies, while from Mexico southward little but O is present. In other parts of the world the data are less adequate but give the impression that ABO frequencies fluctuate much more than the others. Only in a few cases have we adequate data on Rh and MN distribution within countries. In Japan it is clear that ABO frequencies are much more variable than those of the MN groups. In other regions such as India there are unabsorbed enclaves differing greatly in all their blood group frequencies from the surrounding peoples. The same is true of the Americans if we consider the total population and not only the Indians and Eskimos as we did a few minutes ago. Here, however, the reasons are obvious: even if frequencies show as small patches of variation on a topographical map, anthropologically we are concerned with the borderland between two major races, just as we are on the almost straight line that marks the southern edge of the Sahara Desert.

As I have made this summary of the data I have been painfully aware of the lack of precision of my statements: this is a subject where a mathematical treatment is needed which, despite the uneven nature of the data, will measure and compare the amplitudes of the variations. There is, however, no doubt that, in general, the frequencies of the ABO groups do fluctuate more than those of the MN and Rh groups.

We have so far dealt mainly with frequency fluctuations in populated space at one time, the present. We must now consider further how these variations are likely to have originated. We may be tempted to regard them as arising in the manner already suggested, from random frequency fluctuations in relation to time. Even, however, if this accounts wholly or in part for the existing variations in MN and Rh frequencies, the same process, acting at the same time on the same populations, can hardly also account for the much wider variations in the frequencies of the ABO groups. We are therefore led to look for some other process affecting particularly the frequencies of the ABO groups: it requires no great stretch of imagination to see here a probable effect of natural selection.

For many years Sir *Ronald Fisher* and Dr. *E. B. Ford* have held that the existing frequencies of all the human blood groups probably arise mainly from natural selection. Their arguments gained support from the comparison, which I have just summarised, between the distributions of the ABO groups and those of the other systems, but it is only in the past three years that we have begun to see part, at least, of the mechanism whereby

natural selection operates on the blood group phenotypes and hence, ultimately, on the genes.

For many years workers have been collecting data on the frequencies of the ABO blood groups in sufferers from various diseases, and comparing them with the frequencies in the local healthy population. It is now realised that in the resulting mass of published data there are included some accurate and important positive results, but the work as a whole was of varying quality and most of the results were in any case negative so that all the observations tended to be disregarded.

Near the end of this stage of individual and relatively unco-ordinated research came the very important observation by *Struthers* [1951] that among young children dying of bronchopneumonia in Glasgow there was a marked deficiency of group O. The age at which the deaths occurred made it clear that fertility was affected. It is also important, as we shall see shortly, that a bacterial infection was involved.

I ought perhaps to mention here the case of haemolytic disease of the newborn since it was shown by *Levine*, *Katzin* and *Burnham* in 1941 to be very closely related to the Rh blood groups, being the result of incompatibility between offspring and mother, and because it causes numerous deaths in infancy. Apart from the effects of modern therapy, however, the mortality is related almost solely to the Rh gene frequencies in the population and hardly at all to the environment. Similar considerations apply to the rarer form of the disease, resulting from ABO incompatibility between offspring and mother.

The present phase of extensive investigations, carefully controlled and coordinated, was initiated when in 1953 *Aird*, *Bentall* and *Fraser Roberts* produced an adequate amount of sound data showing that the frequency of group A was significantly raised among sufferers from carcinoma of the stomach. These results have been accepted generally, and repeatedly confirmed. They have led to a great extension, mostly on sound lines, of this type of enquiry.

Dr. *Fraser Roberts* will shortly speak to us about blood groups and disease, so I shall mention, very briefly, only one or two further important results.

Sufferers from duodenal ulcer include a very large excess of persons of group O. Moreover, especially among sufferers of group A but also among those of group O, there is an excess of those who lack the secretor gene and hence do not secrete in their saliva the antigens corresponding to their ABO blood group.

There can be little doubt that the occurrence both of gastric carcinoma

and of duodenal ulcer is controlled in part by the nature of the food consumed, and other features of the surroundings may have some effect, such as the psychological environment in duodenal ulcer. Gastric carcinoma is a killing disease but it mainly affects persons past the reproductive period. It must, nevertheless, exert some influence on fertility, especially in males. Duodenal ulcer frequently affects young people: it seldom kills them, but it may do so and hence it too will have some effect on fertility. Thus both these diseases are likely to be means whereby the environment causes a natural selection of the blood group genes and, in the case of duodenal ulcer, of the ABO secretor gene as well. The physiological mechanism whereby the blood groups affect susceptibility to these diseases is at present obscure but it is likely to be related to the secretion by the stomach glands, in salivary secretors, of large quantities of the blood group substances.

Before these examples were discovered it was thought that infectious diseases were more likely than other diseases to be influenced by the blood group of the sufferer, since many infectious bacteria have a coating of polysaccharide closely related in composition to the blood group antigens. In some cases the similarity extends to the reactions of these polysaccharide antigens with specific antibodies. The only established example, however, of a differential incidence of an infectious disease in relation to the blood groups, is that demonstrated by *Struthers*. As already mentioned, he showed that among young children in Glasgow dying of bronchopneumonia, there was a marked deficiency of group O. It must be admitted that bronchopneumonia has hitherto not been regarded as due to any one specific bacterial species. There is, however, no doubt that its incidence and severity are closely related to other features of the environment besides the ambient bacterial flora.

The next stage of investigation must be to look for further examples of diseases which show a preference for certain blood groups and, in diseases where a relation to blood groups is established, to try to discover the mechanism whereby they affect susceptibility.

Gradually, we may hope, such information will be gained until a point is reached where it will begin to dovetail with and explain the regional and racial distribution of the blood groups. That this is not merely a pious hope is shown by the example of another set of simply inherited haematological characters, the haemoglobins. Here it is now certain that heterozygotes for normal haemoglobin and sickle-cell haemoglobin (haemoglobin S) are specially resistant to malignant tertian malaria (*Allison* [1954]) and there can be no reasonable doubt that, through the natural selection, the distribution in Africa and elsewhere of the gene for haemoglobin S is related to

that of the parasite, *Plasmodium falciparum*, which in turn is determined by geographical conditions, and especially the distribution of water suitable for the breeding of mosquitoes.

If such a stage can be reached in the study of the blood groups, the study of these characters will have made a valuable contribution not only to the classification of man, but to our understanding of his evolution.

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Discussion

B. Woolf (Edinburgh): It seems that the apparent relative stability of gene frequencies in the Rh system may conceal quite large selective processes. Haemolytic disease involves selection *against* heterozygotes, which by itself would lead to fixation of the most frequent allele. To explain the apparent stable polymorphism, one must suppose there are other processes involving strong selection *for* the heterozygotes.

Ph. Levine (Raritan, New Jersey): It is suggested that in all studies on relationship of the ABO blood groups and disease, the subgroup of A, i.e. A_1 or A_2, be determined preferably with reagents anti-A_1 specific for A_1 and anti-H (anti-A_2) specific for A_2 and O. Studies including these reagents may possibly reveal more striking discrepancies than hitherto observed.

R. Singer (Cape Town): In connection with Dr. *Mourant*'s paper, I would like to comment on his reference to *Allison*'s theory of the "protection" against *falciparum* malaria conferred by the possession of the sickle-cell haemoglobin. While it is probably true that the sickle cell will flourish only in a malarious region, this alone cannot explain the findings in Africa (e.g. where there is a sharp drop in sickling incidence south of the Zambesi river where malaria has been, and still is, prevalent) and Madagascar. It suggests that factors other than malaria are operating.

A. E. Mourant (London): In reply to Dr. *Levine*, there is a lack of frequency data for A_1 and A_2 in healthy persons but this is gradually being remedied. Most hospital records

give only the four main ABO groups so that only these can be used in retrospective studies, but in some forward studies the A_1 A_2 distinction is being made.

I realize that for stable equilibrium there must be positive selection of heterozygotes. It is at present virtually impossible to distinguish serologically between AO and BO on the one hand and AA and BB on the other, but a search should be made for evidence of differential disease incidence between, for example, AO and AA using, if necessary, pedigree evidence to diagnose the genotypes.

My remarks on the haemoglobins were deliberately oversimplified. Their genetics will be considered more fully at another session.

Levine, Philip: Acta genet. *6*, 515–516, 1956/57

Division of Serology and Immunohematology, Ortho Research Foundation,
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BLOOD GROUPS AND IMMUNOGENETICS RARE RED CELL GENOTYPES—SOME ILLUSTRATIVE CASES

By PHILIP LEVINE

In the past few years, a number of rare genotypes were observed in highly selected bloods submitted for further studies. These belong to several system such as A_4 (A_0), B_w, and O_h of the ABO system, D--/D--, and $r^y r^y$ of the Rh system, $S^u S^u$ of the MNSs system, the high incidence genotypes $Tj^a Tj^a$ and $Ve^a Ve^a$, and the low incidence blood factor Mi^a including the remarkable Di^a. The latter two are most always heterozygous.

In a number of examples such as phenotype O^h and genotype $Tj^b Tj^b$ an unexpected antibody is invariably found in the sera of these rare bloods, i.e. anti-H and anti-Tj^a, respectively. In some of these cases the rare blood is the result of a consanguineous mating, the propositus in the O_h case being homozygous for a suppressor gene x preventing the expression in the particular family studied of the B factor in the red blood cells and in the secretion. In the heterozygous state, the suppressor gene x cannot be detected and this explains the paradoxical situation of a mating nonsecretor O_h

(genotype B_x O_x) by nonsecretor A_1O with two offspring A_1B nonsecretor and O secretor.

Several examples of the low incidence antibody anti-Mi^a were observed in each case associated with hemolytic disease. The V^w factor of *Hart* et al. was shown to be identical with Mi^a. This illustrates the importance of establishing the independence of any presumably new blood factor before it is named. Genetic studies to determine the relationship of Mi^a to the MNSs system are still to be caried out.

The Di^a blood factor is most significant because it is almost completely absent in a caucasoid population but reaches an incidence from 35–40 % in certain Indian tribes of Venezuela and Brazil and 11 % in American Indians and 8 % in Japanese. This raises a very interesting point of a blood factor which in caucasoids is unimportant clinically but which may prove to be very important in other racial groups. Extensive studies were carried out in order to establish that Di^a is independent of other low incidence blood factors.

Galatius-Jensen, F.: Acta genet. *6*, 516–517, 1956/57

The University Institute of Forensic Medicine, Copenhagen, Denmark

ELECTROPHORETIC PATTERN OF HEREDITARY HUMAN SERUM PROTEINS

By F. GALATIUS-JENSEN

At the University Institute of Forensic Medicine in Copenhagen we have adopted the electrophoretic method of *O. Smithies* by which it is possible to discern between 3 different types of human sera apparently genetically controlled.

The great majority of the blood samples in our department are withdrawn outside the Institute and referred to the Institute by mail, and consequently the sera often slightly haemolyzed. It was found that even a very slight degree of haemolysis, so slight that it could not be detected

by the naked eye, obscured the results and made is extremely difficult to discern between the 3 groups. This obstacle however was circumvented by deliberately adding haemoglobin to all sera so that the haemoglobin content became more than 300 mg. per cent. Using those grossly haemolyzed sera it was found that the 3 types were clearly differentiated by the localisation of the haemoglobin on the starch gel. The explanation of this phenomenon is probably that the substances in the serum which bind the haemoglobin and which are differentiated by starch gel electrophoresis are identical with the haptoglobins, first described by *Jayle* 1952.

Accordingly Drs. *Smithies* and *Walker* in a paper, still in press, propose a notation as follows: The system is to be called the Haptoglobin System. The 3 serum types: Haptoglobin 1–1, Haptoglobin 2–1, and Haptoglobin 2–2.

To date we have examined 16 families with 54 children. The figures fully confirm the genetical theory of *Smithies* and *Walker*.

Grubb, R.: Acta genet. *6*, 517, 1956/57

Bacteriological Institute, University of Lund, Sweden

HEREDITARY SEROLOGICAL HUMAN SERUM GROUPS

By R. GRUBB

An account of the investigation will be published in Acta path. microbiol. Scand.

Jonsson, B.: Acta genet. *6*, 518, 1956/57

State Laboratory of Forensic Chemistry, Stockholm, Sweden

THE SUBGROUPS OF P IN AN INVESTIGATION OF TWINS

By B. JONSSON

Material concerning 182 pairs of twins was investigated in our laboratory with special regard to the strength of the P + reactions. The twins were all adults.

100 of the pairs were with all probability one-egg twins and 82 of the pairs two-egg twins.

The diagnosis whether they were one-egg or two-egg twins was made inter alia through multiple similarity and in several cases through obstetrical anamnesis to, and is quite independent of the results of the P investigations.

In the 82 pairs of two-egg twins there were 16 pairs of concordant P-twins, 9 pairs of discordant P-P +twins and 57 pairs of concordant P +twins. In these 57 pairs of P +twins 42 pairs were concordant, 5 pairs probably concordant and 10 pairs clearly discordant in the strength of the P +reactions.

In the 100 pairs of probably one-egg twins there were 24 pairs of concordant P-twins, no pairs of discordant P-P+ twins and 76 pairs of concordant P+ twins. In these 76 pairs of P+ twins, 71 pairs were concordant, 4 pairs probably concordant and only one pair clearly discordant in the strength of the P+ reactions. A control investigation of this pair could not be arranged.

That is: 57 pairs of two-egg P+ twins with 10 pairs discordant in strength and 76 pairs of probably one-egg P+ twins from which one pair is discordant in strength.

The results strengthen the opinion that also the strength of the P+ reaction is in the main genetically caused.

Boorman, K. E.: Acta genet. *6*, 519, 1956/57

S. London Metropolitan Blood Transfusion Centre, Sutton, Surrey, Great Britain

MOTHER-BABY ABO BLOOD GROUP DISTRIBUTIONS

By K. E. BOORMAN

A short commentary on the various ABO blood group distributions of pregnant and post-partum women and their offspring. The material is divided into two major sections according as to whether the mother is Rh Positive or Rh Negative (D+ or D−); in the Rh Negative section (D−) it is sub-divided as to whether or not the mother's serum contains Rh antibodies. Possible explanations of the discrepancies noted are discussed.

Woolf, B.: Acta genet. *6*, 519–520, 1956/57

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ABO INCOMPATIBILITY IN HAEMOLYTIC DISEASE OF THE NEWBORN

By B. WOOLF

In 1943, *Levine* reported that the incidence of haemolytic disease of the newborn due to Rh immunisation of the mother was higher in the offspring of compatible than of incompatible matings on the ABO system, a compatible mating being one in which the mother would tolerate a transfusion of her husband's red blood corpuscles. This finding has been amply confirmed by many workers and a statistical analysis has been made of the published data. In some incompatible matings, such as ♂ AB × ♀ A, half the foetuses will be compatible, and in others, such as ♂ AB × ♀ O, none

will be compatible. The published work is consistent in all respects with the suggestion, put forward by several workers, that the immunising foetus must always or nearly always be compatible, though once the mother is immunised, the subsequent foetuses will be affected whether they are compatible or not.

This phenomenon invites further research. On the biochemical level, the most likely explanation seems to be that the Rh-substance by which the foetus immunises its mother is so closely bound to ABO-substance that, when the latter is neutralised by maternal antibodies, the Rh-substance is completely removed from the circulation. On the pathological level, the question arises whether incompatible foetuses borne by an already immunised mother are or are not less severely affected by haemolytic disease than a compatible foetus. There are conflicting reports on this in the literature. Much information could be obtained by analyses of existing records of blood typing centers.

It is well recognised that haemolytic disease entails selection against heterozygotes in the Rh system. The ABO incompatibility effect results in simultaneous selection of the ABO alleles, weakly against O and strongly in favour of B.

Cotterman, C. W.: Acta genet. *6*, 520–521, 1956/57

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SOMATIC MOSAICISM FOR ANTIGEN A_2

By C. W. COTTERMAN

Just as cellular interchange between dizygotic twin embryos leads to permanent erythrocyte mosaics in cattle, sheep and man, one might expect early somatic mutation to produce blood antigen mosaicism without immune complications. Such appears a likely explanation for 4 cases of "O + A_2" mosaics previously reported (Am. Soc. Human Genetics, East Lansing [1955]) and for an unusual case discovered more recently:

Mrs. Do. gave birth to an A_2B child, yet her own erythrocytes are unquestionably type O. A suspicion that the child had inherited A_2 from

its mother was gained when the latter's serum was found to lack agglutinins against A_2 cells, a characteristic of mosaic $O+A_2$ individuals. As expected, the husband is A_1B, and an older child of this marriage is B. Studies of other tissues and fluids of Mrs. D., and the findings on her collateral relatives, strengthen the supposition that gene A_2 is present in this woman's ovaries and probably in some somatic tissues, though absent or inactive in the erythroblasts.

In other families, mixtures of O and A_2 erythrocytes have been observed in mother and son, and in two sisters, one of whom exhibits a pronounced eye-color mosaic (heterochromia).

Discussion

Ph. Levine (Raritan, New Jersey): At first glance there appears to be a serologic resemblance of B_w and *Cotterman*'s "$O-A_2$" mosaicism. Active eluates from B_w red cells specific for B blood were readily obtained. I should like to inquire whether or not Dr. *Cotterman* studied the specificity and range of activity of eluates from his remarkable "$O+A_2$" blood.

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THE A AND H CHARACTER OF THE BLOOD GROUP SUBSTANCES SECRETED BY PERSONS BELONGING TO GROUP A_2

By W. M. WATKINS and W. T. J. MORGAN

The interaction of genes in the heterozygote has received much attention in relation to hybrid vigour in plants and animals. In man, however, few examples of the interaction of genes at a single locus have hitherto been worked out in biochemical terms. The findings of *Filliti-Wurmser, Aubel-Lesure* and *Wurmser* [1953] on the molecular size of β-agglutinins give an example where it appears that the heterozygote (A,O) produces a product which differs from that produced by either of the genes in the homozygous con-

dition (OO or A_1A_1). A second example relates to the haemoglobins produced in individuals carrying the sickle-cell trait. *Neel* [1949] and *Beet* [1949] put forward the hypothesis that the sickle-cell trait and sickle-cell anaemia occur respectively in individuals heterozygous and homozygous for the same abnormal gene. This gene is now known to be responsible for the production of a haemoglobin which differs in its electrophoretic mobility and solubility from that present in normal individuals, and the sickle-cell gene is an allele of one which produces normal haemoglobin (*Pauling*, *Itano*, *Singer* and *Wells* [1949]). In the cells of individuals heterozygous for this condition, that is, those carrying the sickle-cell trait, both the abnormal and normal types of haemoglobin are found to be present in the erythrocytes. In this example, therefore, each allele appears to give rise to its own characteristic product in the heterozygote and there is no interaction of the genes.

A further example of the product of allelic genes has recently been examined (*Morgan* and *Watkins* [1956]). According to the blood group of the individual, substances possessing group A, B and H properties occur in a water-soluble form in the secretions and tissue fluids of about 80% of individuals. The nature of the product of the blood group *A* and *B* genes in individuals belonging to group AB was studied in an attempt to determine whether the secretions in these heterozygous individuals contain molecules which carry both A and B specific groupings or whether they contain a mixture of molecules some of which carry A and others B specificity.

The A and B substances are very similar in their chemical and physical properties (see *Kabat* [1956]). They both belong to the class of compounds known as muco-polysaccharides and are composed of the same four sugars, L-fucose, D-galactose, N-acetyl-D-glucosamine and N-acetyl-D-galactosamine and eleven amino acids. This close similarity does not allow the usual fractionation procedures, including electrophoresis and ultracentrifugation, to be applied successfully to their separation and therefore the method used to obtain evidence on the nature of the AB substance was one which involved the use of serological precipitation tests. As we wished to investigate the possibility that the *A* and *B* genes co-operated in the heterozygote to produce a product which differed from that arising from either gene alone it was first of all necessary to show that an artificial mixture of A and B substances could be separated by the method used. It was found that when a precipitating rabbit anti-A serum or a purified extract of Sieva lima beans, which contained powerful anti-A precipitins, were added to such a mixture the A activity, as measured by agglutination inhibition

tests, was carried down in the precipitate leaving a supernatant solution which was free from A activity but which gave the same inhibition titre against anti-B serum as the original mixture. When the thoroughly washed precipitate was dissolved in alkali, neutralised and heated to destroy any remaining antibody the solution was found to possess only A activity. These findings, therefore, demonstrated that it is possible to separate an artificial mixture of A and B substances by the precipitation technique. Applications of this method to cyst substances and salivas obtained from individuals belonging to group A_1B and group A_2B revealed that after removal of the precipitate the supernatant solution showed an almost complete loss of B activity in addition to loss of A activity and the precipitate possessed both A and B activities in the same ratio as the original solution. When rabbit anti-B serum was used as the precipitating reagent both A and B activities were again carried down in the precipitate from the AB substances whereas only B activity could be detected in the precipitate from the artificial A and B mixture. These experiments therefore indicated that in the tissue fluids and secretions of secretors belonging to group AB, a large proportion if not all, the macromolecules showing blood group specificity possess both A and B properties. In this instance, therefore, the allelic genes appear to collaborate in producing the gene product in the heterozygote (AB) to give materials which differ in molecular nature, although not in general specificity, from the product arising from either gene in the absence of the other.

The results obtained in the experiments outlined above show the information which can be gained on the molecular nature of materials by the application of the simple technique of serological precipitation. It was therefore decided to apply this method to substances showing H specificity (*Watkins* and *Morgan* [1955]). The genetical relationship of the H character to the products of the *A*, *B* and *Lewis* genes has not yet been elucidated and it is therefore of considerable interest to know whether the H activity which is found in the secretions of secretors belonging to group O, but which can also be found in the secretions of individuals belonging to group A, B or AB, is, in the latter group of individuals, present as a free molecular entity or whether there are molecules present which show both A and H, or B and H, or A, B and H specificies. Since the secretions of group A_2 individuals possess considerable H activity our preliminary studies have been carried out with these materials. In order to obtain a complete picture of the types of specific molecules present it is necessary to work with native secretions because if purified preparations are used they may represent only part of blood group specific moieties present in the original fluid. For this reason

all our experiments have been made on untreated cyst fluids or saliva samples. Three cyst fluids from A_2 individuals and three A_2 saliva samples have been examined using rabbit anti-A and anti-H sera as the precipitating reagents. An artificial mixture of A and H substances was included as a control in each experiment. Titration of the redissolved precipitates obtained from the A_2 secretions revealed in each instance the presence of H activity as well as A activity whereas the precipitate from the artificial mixture showed only the activity homologous to the precipitating reagent. These results therefore show that in A_2 individuals molecules are present in the secretions which carry both A and H activity. Following precipitation with anti-A serum the supernatant solutions from the A_2 secretions usually showed some H activity although the A activity had been completely removed. This result thus indicates that there are some free H molecules present in the secretion as well as those possessing both A and H activity. Owing to the less satisfactory nature of the precipitating rabbit-anti-H sera available to us it has not been possible to establish with any certainty whether there are also free A molecules which do not show H activity but further experiments are being carried out to clarify this point.

These studies will have to be extended to large numbers of secretions before any genetical conclusions can be based on the results. It is however of interest to speculate on the possible interpretation of the finding that molecules showing both A and H specificity exist in the secretions of A_2 individuals. In the earlier example investigated the product derived from AB persons, which was shown to be composed of molecules carrying both A and B specific groupings, was known to arise from the action of allelic genes. It seems improbable, however, that the H activity which has been shown to be associated with the A molecules in the A_2 secretions is produced by a gene allelic to *A*. The genotype of the A_2 examples investigated was unknown and they could, therefore, have each obtained from a person of genotype A_2O and the H character could have resulted from the presence of the *O* gene. It is known however that red cells of individuals homozygous for the A_2 gene i.e. A_2A_2, also give strong reactions with anti-H sera and the H character would therefore appear to be in some way directly related to the presence of the A_2 gene. A second possibility is that H is a partial antigen produced by the A_2 gene in addition to the A antigen. *Wiener* and *Wexler* [1952] have discussed partial antigens arising from the action of one gene and consider that the O (H) character of A_2 red cells can be explained on this basis. If this were the explanation, however, one would perhaps not expect to find free H molecules in the secretions of A individuals as well as AH molecules. A third possibility, which appears to us to be the

most likely, is that H is a basic substance on which the *A* and *B* genes imprint their characteristic specificity. If this idea is correct then it seems possible that the genes A_1, A_2 and *B* act late in the synthesis of the group specific substances and control the final stages only of the conversion of a common precursor, H substance, into the strictly group specific gene product. If the gene A_2 is assumed to be less effective in bringing about the conversion of H to A than the A_1 gene, one would expect the product in A_2 individuals to have more H character than that produced in A_1 individuals and also to find a certain proportion of H molecules which were unchanged, as has been found experimentally. When the genes A_1 and *B* act together one would expect an almost complete conversion of the precursor into a mucopolysaccharide material which possesses both A and B specificity but has very little H character and as both genes would be competing for the same substrate the appearance of molecules showing dual specificity could be accounted for. The conversion by enzymic action *in vitro* of A and B substances into materials devoid of their original specificity but possessing H specific character has recently been accomplished (*Iseki* and *Masaki* [1953], *Iseki* and *Ikeda* [1956], *Watkins* [1956]) and this finding lends support to the idea that H is a basic substance. The fact that the haemoglobin genes each produce their own characteristic product in the heterozygote whereas the *A* and *B* genes give rise to a joint product might be due solely to the stage at which the influence of the genes enters into the synthesis of the final product.

Further studies using secretions from individuals of known genotype should reveal whether the molecules present in an A_2O person differ from those in an A_2A_2 and whether the H character shown by A_1, B and AB secretors is also part of a complex macromolecule. If the limitations of the precipitation technique force us to seek other means of demonstrating the multiple specificity of simple molecules we feel that the examination of this problem by electrophoresis of antigen-antibody complexes in agar gel could be utilised as this method would dispense with the necessity of having a precipitating antibody. One might anticipate that on electrophoresis the heterologous specificity would migrate with the homologous antigen-antibody complex if both specificities were carried on the same molecule whereas if it were a free entity it would move independently. Section of the agar gel into strips, freezing and thawing and examination of the liquid which separates from the agar by the usual agglutination inhibition tests should reveal the position of the various components. Use of this method might also give information about the relationship of the H character to the products of the Lewis genes.

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GENE FREQUENCIES IN TWO BRAZIL-INDIAN TRIBES

By H. KALMUS

Gene frequencies in two Brazil-Indian tribes, tasting thresholds, colour vision, sickling and six systems of blood factors were investigated in two Brazilian tribes, the Kaingangs and the Carajas, some 1,000 miles apart. Gene frequencies have been calculated by the method of "original parents" and the results are compared with those obtained in related or neighbouring groups. The new antigenic Diego factor was frequent in both groups and its anthropological and possible pathogenic importance is discussed *. Detailed results are being published in the Annals of Human Genetics.

* New Diego data, as yet unpublished, of other ethnic groups are presented for comparison.

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SERO-ANTHROPOLOGICAL INVESTIGATIONS IN THE WALSER AND ROMANSH ISOLATES IN THE SWISS ALPS AND THEIR METHODOLOGICAL ASPECTS

By J. K. MOOR-JANKOWSKI and H. J. HUSER

The geographical, social and political situation of the high alpine valleys of Grisons in Switzerland caused the formation of numerous isolates and their preservation throughout centuries and, partly, until today.

The inhabitants of these isolates may be divided into the autochtone Romansh speaking population and the German speaking Walsers, who immigrated into the Grisons in the thirteenth and fourteenth centuries from the Valais (*Joos* [1946]).

The Walsers itself can be divided, on linguistic grounds, into two main groups, the Eastern und the Western Walsers (*Hotzenköcherle* [1944]).

The Eastern Walsers have mixed to some extent with the neighbouring peoples, whereas the Western Walsers maintained a much stricter endogamy.

There has been very little mixing of the Romansh people of the examined villages with any outside group and they may therefore be regarded as representing the local non-Walser population.

During the years 1948 to 1955 serological tests were carried out on approximately 1,600 Eastern Walsers and 2,300 Western Walsers, i.e. the inhabitants of all the 21 Walser villages in Switzerland, and, as controls, on 600 inhabitants of 4 Romansh villages.

The examined population represents about 80% of the entire population of the examined villages; the remaining 20% consisted of people

absent or gravely ill at the time of investigation; only about 5% of the entire population refused to be examined. Thus the results may be considered as representative for the population examined.

The investigation carried out by the authors represents about 70% of the whole material presented; the additional results of other authors have been carefully reviewed and, if necessary, corrected before being included in the computed material.

1,100 individuals were examined for ABO; 1,000 for ABO and Rh-standard (D); 2,400 for A_1A_2BO, Rh (C, c, D, E) and MN, among which 300 additionally for K and Fy^a; 150 were tested for A_1A_2BO, Rh (C, C^w, c, D, D^u, E, e) MNS, Henshaw, P, Lu^a, K, Le^a, and Fy^a.

The serological tests were performed by the investigators, and also by the Swiss Red Cross Blood Transfusion Centres Berne (Dr. *Hässig*) and Basle (Dr. *Holländer*), by Laboratoire d'analyses médicales et biologiques in Geneva (Dr. *Steinmann*) and by the Blood Group Reference Laboratory in London (Dr. *Ikin* and Dr. *Mourant*).

The investigations were made possible by the grants from the Swiss National Fund for Scientific Research and also by the help of Dr. *A. E. Mourant*.

Anthropological measurements and observations were carried out by *K. Hägler* and *H. Kaufmann* on about 60% of the serologically tested individuals.

We do not intend to present here our complete results, which will be published shortly elsewhere (*Moor-Jankowski, Huser, Rosin* [1957]); we only wish to give a general survey of the serological situation of the populations examined and to insist on the methodological aspects of sero-anthropological investigations in isolates as derived from the experience of our rather extensive study.

Anthropo-Serological Situation of the Walser and Romansh People

The examined isolates of the Swiss Alps display an *extreme and often highly significant variability of blood group frequencies* (*Huser, Moor-Jankowski, Rosin* [1956]). The common characteristic to be found in almost *all Walser isolates* is the *low frequency or absence of* A_2.

The more endogamous *Western Walsers* show as a common serological characteristic the *high O frequency*, in fact the highest ever found among white people, and this for about 2,300 people examined in 15 villages. In most villages, gene O was found in 75 to 81 and more % of the subjects

tested. The same population also shows *a gene B frequency of less than 4%* in the more isolated and endogamous villages.

The less endogamous *Eastern Walsers* show a *great variability of ABO frequencies*, with some villages reaching 80% of gene O and others displaying rather low O, and high A frequencies. The frequency of B varies from one village to another.

Both the Eastern and the Western Walsers show *highly significant differences in the Rh-factor (D) distribution from one village to another*, some villages with an Rh- (dd) of over 25% and some where the Rh- (dd) frequency is lower than the Swiss average.

The *Romansh isolates* correspond to the Swiss average as regards ABO, but show rather lower Rh^- (dd) frequency, though there is much less variability to be found than in the Walser isolates.

In conclusion we found in most of the 25 Walser and Romansh isolates tested *significant differences from the Swiss average and from each other, though there are also some common characteristics in the isolated populations.*

The results of our investigation raise of course several problems, which will be discussed elsewhere. At this Congress, however, we should like to stress only *the methodological aspects* of such investigations in the belief that they may be of importance for the further work in this field.

The essential methodological conclusions issuing from our investigation may be summed up as follows:

1. Serological Tests are to be Carried Out Only in Qualified Laboratories

Though this requirement seems to be self-evident, there has been quite recently some important sero-anthropological work on the Rh-frequencies done by slide tests in the field without any laboratory control, and the high Rh-negative (dd) frequencies found were probably due to the inadequate technique only.

We feel obliged to refer here to our own experience with 137 individuals tested by advanced medical students with the slide technique in the field: 8 persons found negative subsequently, in the laboratory, proved to be positive; in addition, one was found to be of type D^u.

We therefore suggest that all serological results of sero-anthropological investigations without qualified laboratory tests be excluded from any serious discussion and computation.

2. Exact Determination of Endogamy Based on the Study of Pedigrees

When examining isolates or supposed isolates, great importance must be attached to the exact determination of endogamy. For this reason

pedigrees of as many generations as possible are to be established. Our experience has shown that the inhabitants of an isolate are generally in a much higher degree endogamous than might be supposed from their present and known relationship. Such a situation, which is caused by the small number of ancestors of all the inhabitants, cannot be determined by recording the cousin marriages only.

In fact, from the genetic point of view, some people may be as closely related by their common ancestors as first cousins are, and yet appear as distant relatives only. A striking example of such a situation is the pedigree of ten generations from the Walser village Bosco-Gurin.

3. Statistical Determination of the Influence of the Size of Families on the Blood Group Distribution in the Isolates

Dr. *Frazer Roberts* gave the first impulse to consider the question of adequate statistical tests for entire populations of isolates, to whom the current X^2 test for statistical analysis of random samples cannot be applied.

The standard error in the estimates of the blood group gene frequencies cannot be found with the usual formulae for unrelated individuals, as the data will comprise many families and related persons. This will make the estimates much more variable. For example, if two parents happen to be both O, and have many children, all these children must necessarily be O, but if an equal number of persons were chosen at random, instead of a group of brothers and sisters, they would most unlikely *all* be O.

Dr. *Cedric A. B. Smith* has very kindly helped us in this problem, and we are greatly indebted to him for this part of our communication. He has, in fact, provided a method for correcting part of the above-mentioned effect, by giving formulae for the variances of the numbers of different blood groops when there are families of different sizes within the population.

However, these formulae must be used with caution, firstly because they only take into account the closest degrees of relationship, viz. brothers and sisters, but not parents and children, nor the further amount of inbreeding caused by different related families.

Also, the ideal method of analysis is yet to be found for the case that samples of a large part of populations, or nearly complete populations are concerned. In the presence of two small samples from different populations, a statistical test of heterogeneity will tell whether there is reason to suspect that the blood group frequencies are different. But when virtually the entire population is known, it would be unreasonable to expect frequencies to be *exactly* the same in two populations, because there will be a small random variation from one generation to the next in any case.

The question arises what variation there is to be expected from this cause. This is a problem of population genetics, not of pure statistics; it cannot be answered by an ordinary statistical significance test.

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BLOOD GROUP FREQUENCIES IN FRENCH BASQUES

By L. E. NIJENHUIS

Mourant's hypothesis that the European population should be composed of a proto-Basque Rh negative component with no or little B and an Eastern Rh-positive component with much B is well known.

In order to test this theory by determining the other blood group systems, we collected a series of blood specimens from French Basques. Special attention was given to the *Duffy* blood group, as the percentage of Fy(a+) in Western Europe is known to be relatively high whereas in Asia, this percentage is particularly high. Following *Mourant*'s train of thought, we should therefore expect a lower frequency of Fy(a+) in Bas-

ques than is normally found in the other regions of Western Europe. Thanks to the active cooperation of the Blood Transfusion Service in Biarritz under the direction of Dr. *Souchard*, we have been able to collect a series of 484 blood samples. We found the following results:

Table 1

ABO		N = 484	
O	58.26%	Gene frequencies	
A_1	31.31%	O	0.764
A_2	9.18%	A_2	0.057
B	0.83%	A_1	0.173
A_1B	0.00%	B	0.006
A_2B	0,41%		

A remarkable finding was the low percentage of B and AB. On inquiry it was found that all 6 persons carrying the B antigen were not of pure Basque origin. *Eyquem*, who tested pure (French) Basques, also in the south of France, did not find any B or AB. This might indicate that the B antigen has been lacking in the original pure Basque population and that the low percentage of B, found by most investigators, is the result of a mixture with non-Basques. The very low percentage of B we found, proves that our material was composed of rather pure Basque individuals.

As it was to be expected, the MNS system shows no difference in comparison with the findings in other West European areas.

Table 2

MN frequencies		n = 471	
M	28.238%	Gene frequencies	
MN	49.045%	M	0.5276
N	22.718%	N	0.4724
MNS		n = 83	
MMS	28.92%	MS	0.240
MMss	12.05%	Ms	0.288
MNS	21.69%	NS	0.107
MNss	15.66%	Ns	0.366
NNNS	8.43%		
NNss	13.25%		

Table 3

Rhesus			
D factor		n = 482	
D + 79.46%		D = 0.5468	
D — 20.54%		d = 0.4532	
		n = 398	
ccddee	18.84%	gene frequencies	
CcD^{u}ee	0.00%	cde	0.4565
CCD^{u}ee	0.25%	cD^{u}e	0.0000
Ccddee	1.01%	Cde / CD^{u}e	0.0137
CcDee	42.46%	cDe	0.0087
CCDee	19.35%	CDe	0.4285
CcDEe	5.53%	C^{w}De	0.0025
ccDEe	10.39%	cDE	0.0900
ccDEE	0.92%		
ccD^{u}ee	0.00%		
ccDee	0.75%		
C^{w}cDEe	0.25%		
C^{w}CDee	0.25%		

When considering the Rh system we see a percentage of D-negatives which is rather low for Basques. Other investigators have found much higher frequencies, *Eyquem* [1950] even more than 42 %.

Table 4

Factor P		n = 484	
P+	72.93%		
P—	27.07%		
Kell		n = 317	
K+	10.09%	K	0.052
K—	89.91%	k	0.948
Duffy		n = 452	
Fy (a+)	57.08%	Fy^{a}	0.345
Fy (a—)	42.92%	Fy^{b}	0.655

The results of the factors P and Kell did not reveal great differences with the findings in other regions of Western Europe. The frequency of the Fy(a+) however, is significantly lower than in the rest of Western

Table 5

Basque component = 1 — X	
Eastern component = X	
d) English (*Race* and *Sanger* 1950, n = 1798)	0.41
d) Basques	0.47
d) Eastern component	0.00
0.47 (1 — X) = 0.41	
X = 0.128	
1 — X = 0.872	
Fy^a (gene frequency)	
English (*Ikin* et al. 1952, n = 1166)	0.413
Basques	0.354
Eastern component	Y
0.872 × 0.345 + 0.128 Y = 0.413	
Y = 0.875	
Eastern component	
Fy^a = 0.875	Fy (a+) = 98.44%
Fy^b = 0.125	Fy (a—) = 1.56%

Europe. The average percentage of Fy(a+) in Western Europe is about 64%. In order to check whether the percentage of Fy(a+) corresponds to our expectations, regarding *Mourant*'s hypothesis, we made a small calculation.

From the frequencies of the d gene in Western Europe and in the Basques, we may calculate the rate of the Eastern component that has to be added to the Basques we tested in order to get the average frequency of the factor d in Western Europe.

From the rate of this component and the gene frequencies of the factor Duffy in Western Europe and in the Basques, we calculate the expected percentage of Fy(a+) in the Eastern component. This percentage, 98%, seems to correspond very well with the percentage found in East Asia. The frequency of the factor Duffy we found in the French Basques supports therefore *Mourant*'s hypothesis. However, the relations of Rh-frequencies are very complicated in the Basques, as well as in Europe, North Africa and South West Asia. Among other things we have to search for an explanation of the great differences in the percentages of D-negatives between different groups of Basques and the relative homogeneity in this regard in the other parts of Western Europe. It must be right that the present Basques are also a mixed population which *Mourant* supposes to be composed of a proto-Basque D-negative component and a preponderant D-

positive component, which should be found in its purest form in the north of Sardinia. However, the mixture of both these components must be rather heterogeneous, whereas the mixture of the proto-Basque and the Eastern component in the much larger area of the rest of Western Europe must have been more homogeneous. A possible explanation might be found if we assume that the European as well as the Basque mixed populations would have been composed originally of 50% of D genes and 50% of d genes. The population would then have been evenly balanced. Haemolytic disease of the newborn would have eliminated, absolutely and relatively equal quantities of D and d genes. This equilibrium however is labile. If the frequency of the D gene was or became dominating the d gene to a less degree, haemolytic disease would have had a relatively selective influence on the D gene and the more so, as the d gene became gradually less frequent and the difference between the frequencies of D, respective d, greater. In the Basques the opposite effect would have taken place. The frequency of the d gene may have dominated the D gene in certain regions. In regions where the dominance of the d gene became fairly increased, the selective action of haemolytic disease might have been explosive; for, if the frequencies of the d gene increases, the percentage of D-incompatible matings will increase even more which results in an accelerated process of the selection due to haemolytic disease. If, however, the frequency of the d gene decreases, the percentage of D-incompatible matings decreases too and this will check the rate of the selective action. Maybe this mechanism has contributed to a certain homogeneity of the percentage of D-positives in Europe, whereas in the country of the Basques high percentages of D-negative could develop locally.

Finally we have to consider the possibility that genetic drift has played a part in the Basques, thus leading to a locally enhanced selectivity due to haemolytic disease. It should also be considered, how far genetic drift might have been responsible for all other differences between Basques and the people of the rest of Europe, i.e. the absence or decreased frequency of the factor B and the reduced frequency of the gene Fy^a. It would be interesting to determine the Duffy frequencies also in other groups of Basques in order to know if there is some correlation with the frequency of the factor D. It would be of equal importance to test the population of North Sardinia for the Duffy frequencies.

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BLOOD GROUP GENETICS OF THE BASQUES OF IDAHO

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The Basques, like other historically well defined groups such as Lapps and Eskimos, present an interesting congruence of a unique language with a racially distinct population, which has an unusually discrete delimitation from contiguous populations. The homeland of the Basques is in the region of the Pyrenees Mountains and coastlands, but sizeable groups have migrated to both North and South America. The Basque population of the state of Idaho in the western United States is the subject of this blood group investigation. Among the objectives of our study were: (a) estimation of the gene frequency ratios of various blood groups; (b) examination of special questions such as the possible excess of MN groups, the frequency of A_2 and of Rh negative (cde/cde) and their familial inheritance; (c) a comparison of the different generations within the sample; (d) the effect of related individuals in the sample; and (e) a comparison of this population with other Basque populations. The well-informed respect of the Basques for their own interesting population history makes them eminently cooperative subjects for this kind of research.

Origin and Composition of the Population

Although a few Basques entered Idaho as early as 1873, most of the population did not begin arriving until after 1900. The foreign-born Basques typed in Shoshone and Boise, Idaho, came over from the Spanish province of Viscaya mostly before 1924. In the absence of accurate census data local informants estimate some 3,500 Basques living in southwestern Idaho and neighboring areas of eastern Oregon and northern Nevada. A large number, in excess of 2,000 live in Boise, the capitol city of Idaho. While sheep

herding remains an important occupation many Basques have entered various trades and professions but still retain their ethnic ties, speaking Basque and seldom marrying outside their own group.

This paper reports the results of blood group determinations done in 1954 on 163 Basques who volunteered their services as a result of an intensive recruitment program undertaken by leaders of the local Basque community. Of the 163 individuals typed, 113 were obtained in the Shoshone district, a small sheepherding center where most of the subjects came to the study in 32 nuclear family groups. Of these individuals 23 were born in Spain and 90 were born in the U.S.A. The other 50 subjects were obtained in Boise, where the conditions of recruitment favored young, single men, recently immigrated from Spain. Thirty of the 50 were born in Basque provinces of Spain, mostly Viscaya. Only 2 family groups entered the Boise sample.

Table 1. A–B–O and M–N blood groups in the entire shoshone, Idaho, Sample

Blood Group System A-B-O	Observed number	Observed per cent	Expected number	Expected per cent
O	52	46.02	50.23	44.45
A^1	34	30.09	32.74	28.97
A_2	19	16.81	21.82	19.31
B	4	3.54	5.73	5.07
A_1B	0	0.00	1.38	1.22
A_2B	4	3.54	1.10	0.97
Total	113	100.00	113.00	99.99
x^2	0.4808 with 3 D. F.			
M–N				
M	20	17.70	24.86	22.00
MN	66	58.41	56.29	49.81
N	27	23.89	31.85	28.19
Total	113	100.00	113.00	100.00
x^2	3.3636 with 1 D. F.[3]			
(1)	Gene frequencies (2) [2]			
r	.6667	.0334	m	.4691	.0332
Pl	.1644	.0255	n	.5310	.0332
P_2	.1318	.0252			
q	.0370	.0118			
Total	0.9999			1.0001	

1. Maximum likelihood method of *Stevens* [1938].
2. Gene counting method of *Boyd* [1950], p. 395.
3. Slightly greater than P. 05.

Table 2. Rh blood groups in the entire Shoshone, Idaho sample

Most Probable Genotype *Fisher*	Genotype *Wiener*	Observed number	Observed per cent	Expected [1] number	Expected [1] per cent
cde cde	rr	24	21.24	22.16	19.61
CDe cde	R_1r	20	17.70	22.48	19.90
CDeCde	R_1r'	16	14.16	12.46	11.03
Cde cde	$r'r$	24	21.24	20.33	17.99
Cde Cde	$r'r'$	3	2.65	4.68	4.14
cDE cde	R_2r	6	5.31	6.35	5.62
cDE cdE	R_2r''	7	6.19	7.35	6.51
cDe cde	R_0r	5	4.42	4.61	4.08
CDe cdE	R_1r''	6	5.31	11.12	9.84
CDe CDE	R_1R_z	1	0.89	0.79	0.70
cdE cde	$r''r$	1	0.89	0.45	0.40
CdE cde	r_yr	0	0.00	0.21	0.19
Total		113	100.00	112.99	100.01

Gene frequencies [2]

cde–r	.4429
CDe–R_1	.1860
Cde–r′	.2032
CDE–R_z	.0089
cDE–R_2	.1105
cdE–r″	.0045
cDe–R_0	.0439
Total	.9999

$x^2 = 4.9841$ with 4 D. F.

[1] *Boyd, W. C.* [1954].
[2] *Mourant, A. E.* [1954], p. 224–232.

Considered as a single sample, 131 pure Basques, 24 part-Basques and 8 non-Basques were typed. Although members of 72 families are included, a high degree of relatedness is a major characteristic of this sample. This is reflected in the occurrence of large family lines including one containing 23 members spanning 4 generations. At the same time, there is no evidence of inbreeding.

Considered as a Mendelian population the sample of the Basque community of Shoshone necessarily includes those non-Basques who have contributed to the gene pool. For analytical purposes an estimate of the gene frequencies of only pure Basques was also made. Thus, a Basque in this study means a person who had two parents who spoke Basque and an ancestral origin in the Bay of Biscay.

Table 3. A–B–O and M–N blood groups based on the randomly selected sample of individuals, related no closer than r .125, drawn from the Shoshone, Idaho sample

Blood Group System A-B-O	Observed number	Observed per cent	Expected number	Expected per cent
O	10.67	41.40	10.97	42.56
A_1	6.44	24.99	6.63	25.73
A_2	6.11	23.71	6.40	24.84
B	1.11	4.31	1.21	4.70
A_1B	0.00	0.00	0.26	1.01
A_2B	1.44	5.59	0.30	1.16
Total	25.77	100.00	25.77	100.00
x^2	0.0429 with 2 D.F.			
M–N				
M	4.22	16.38	4.64	18.01
MN	13.44	52.15	12.59	48.85
N	8.11	31.47	8.54	33.14
Total	25.77	100.00	25.77	100.00
x^2	0.1167 with 1 D.F.			

Gene frequencies

(1)			(2)		
r	.6523	.0769	m	.4245	.0686
p_1	.1440	.0538	n	.5755	.0686
p_2	.1687	.0623			
q	.0350	0.265			
Total	1.0000			1.0000	

1. Maximum likelihood method of *Stevens* [1938].
2. Gene counting method of *Boyd* [1950], p. 395.

Nature of the Tests

A suspension of fresh red cells was prepared from ear punctures. All tests except those for M and N were performed in tubes. All type A reactions were further tested with absorbed human type B serum, anti A_1 and with a 10% saline extract of *Ulex europeus* seeds (*Boyd* and *Shapleigh* [1945]). The lectin in the Ulex extract detects the H antigen which is present in relatively large amounts in type O and type A_2 red cells. The M and N tests were performed in well slides using immune rabbit sera. The Rhesus test included anti-D (Rh_0), C (rh′), and E (rh″), all of saline antibodies, and anti-c (hr′) and anti-e (hr″) which were albumin or incomplete antibodies. These tests

Table 4. Rh blood groups based on the randomly selected sample of individuals, related no closer than r .125, drawn from the Shoshone, Idaho, sample

Most Probable Genotype *Fisher*	Genotype *Wiener*	Observed Number	Observed per cent	Expected [1] number	Expected [1] per cent
cde/cde	rr	9.22	35.78	8.21	31.86
CDe/cde	R_1r	3.56	13.79	6.89	26.74
CDe/CDe	R_1R_1	3.44	13.36	2.57	9.97
Cde/cde	r′r	4.56	17.67	3.71	14.40
Cde/Cde	r′r′	0.89	3.45	0.42	1.63
cDE/cde	R_2r	0.66	2.59	1.07	4.15
CDe/cdE	R_1r''	0.78	3.02	0.94	3.64
CDE/CDe	R_zR_1	0.00	0.00	0.00	0.00
cdE/cde	r″r	0.11	0.43	0.14	0.54
cDe/cde	R_0r	1.33	5.17	1.19	4.62
CdE/cde	r_yr	0.00	0.00	0.03	0.12
cDE/cDE	R_2R_2	1.22	4.74	0.60	2.33
Total		25.77	100.00	25.77	100.00

Gene frequencies [2]

cde–r	.5646
CDe–R_1	.2129
Cde–r′	.1276
cDE–R_2	.0506
cdE–r″	.0048
cDe–R_0	.0395
CDE–R_z	.0000
Total	1.0000

$x_2 = 2.2575$ with 2 D.F.

[1] *Boyd, W. C.* [1954].
[2] *Mourant, A. E.* [1954], p. 224–232.

were incubated in a water bath at 37° C. for one hour and then centrifuged at low speed. Negative and positive controls were employed, at least two persons read each test and a number of specimens picked by random numbers were retested for concordance.

Blood Groups and Gene Frequencies of the Shoshone Sample

Tables 1 and 2 indicate that the values secured in this sample are in general agreement with values from other Basque series. The frequency of B is low, and a large proportion of A is A_2. The frequency of the gene for N is slightly higher than in many European populations. Similarly the gene frequency of the cde group (rr) is higher than in most European populations,

although not as high as that reported in some other Basque studies (*Mourant* [1954]).

In order to examine the effect of the relatedness of individuals in the sample, two more estimates of gene frequencies were prepared. The coefficient of relationship of each person to all other persons in the sample was computed (*Li* [1955]) and the persons with an r value of 0.125 or less were considered unrelated. An equivalent artificial sample was then selected by random numbers from the thusly defined unrelated persons. Analysis of these is exhibited in tables 3 and 4. These tables show a rise as compared with tables 1 and 2 in the frequency of three of the critical genes in Basque populations: A_2, N and Rh negative (cde/cde). Tables 5 and 6, based on pure Basques only, show values most similar to those in tables 3 and 4.

Table 5. A–B–O and M–N blood groups in a sample of Basques from Shoshone, Idaho, related no closer than r .125 (randomly selected sample)

Blood Group System A-B-O	Observed number	Observed per cent	Expected number	Expected per cent
O	9.89	50.28	8.94	45.45
A_1	3.56	18.10	3.41	17.34
A_2	4.56	23.18	5.69	28.93
B	0.10	0.51	1.16	5.89
A_1B	0.00	0.00	0.16	0.81
A_2B	1.56	7.93	0.31	1.58
Total	19.67	100.00	19.67	100.00
x^2		0.1851 with 1 D.F.		
M–N				
M	3.33	16.93	3.49	14.74
MN	9.89	50.28	9.59	48.75
N	6.45	32.79	6.59	33.50
Total	19.67	100.00	19.67	99.99
x^2		0.0181 with 1 D.F.		

(1)	Gene frequencies		(2)		
	.07642	.0271	m	.4209	.0787
p_1	.0951	.0159	n	.5790	.0787
p_2	.1883	.0252			
q	.0424	.0109			
Total	1.0000			.9999	

1. Maximum likelihood method of *Stevens* [1938].
2. Gene counting method of *Boyd* [1950], 0.395.

Table 6. Rh blood groups in a sample of Basques from Shoshone, Idaho, related no closer than r .125 (based on the randomly selected sample)

Most Probable Genotype *Fisher*	Genotype *Wiener*	Observed number	Observed per cent	Expected [1] number	Expected [1] per cent
cde/cde	rr	5.79	29.44	5.33	27.09
CDe/cde	R_1r	3.44	17.49	4.01	20.39
CDe/CDe	R_1R_1	2.33	11.85	1.57	7.98
Cde/cde	r′r	4.44	22.57	3.51	17.84
Cde/Cde	r′r′	0.00	0.00	0.58	2.95
cDE/cde	R_2r	0.37	2.90	1.28	6.51
CDe/cdE	R_1r''	0.44	2.24	1.17	5.95
CDE/CDe	R_zR_1	0.00	0.00	0.00	0.00
cdE/cde	r″r	0.11	0.56	0.07	0.36
cDe/cde	R_0r	1.33	6.76	1.23	6.25
CdE/cde	r_yr	0.00	0.00	0.02	0.10
cDEc/DE	R_2R_2	1.22	6.20	0.90	4.58
Total		19.67	100.01	19.67	100.00

Gene frequencies [2]

cde–r	.5220
CDe–R_1	.1594
Cde–r′	.1711
CDE–R_z	.0000
cDE–R_2	.0885
cdE–r″	.0019
cDe–R_0	.0571
Total	1.0000

$x^2 = 0.6532$ with 2 D.F.

[1] *Boyd, W. C.* [1954].
[2] *Mourant, A. E.* [1954], p. 224–232.

Thus it appears that the inclusion of closely related persons may make an important difference in the estimate of the gene frequencies.

In the Boise sample only 2 family groups were included to begin with and so the correction for relatedness made no major difference with gene frequencies.

These figures may serve to call attention to a ubiquitous problem in anthropological studies of small groups. While our basic formulas assume unrelated persons in a random breeding population, such a sample is difficult to obtain in most populations and virtually impossible in small groups. One cure for such a situation is to specify the coefficient of relationship of those members of the group drawn in the sample. In the present instance this leave us with a diminished series and a set of data for which strictly comparable data on other Basque groups are not available.

Differences Between Generations

The blood groups of the third and fourth generation show a rise in the frequency of A_2 (from p_2 of .1071 to .1574) but otherwise an overall stability. With reference to the Rh types, the greatest generation differences lie in the decrease of cde/cde (rr) from 22 % (cde = .4444) in the third generation to 12 % (cde = .3870) in the fourth generation, in CDe/cde (R_1r) from 19.44 % (CDe = .2213) in the third generation to 14.00 % (CDe = .0946) in the fourth generation and in Cde/cde (r′r) from 19.44 % to 30 % or Cde = .1815 to .3373.

In calling attention to these differences it must be noted that a trend

Table 7. A–B–O and M–N blood groups of third generation individuals in the Shoshone, Idaho, sample

Blood Group System A-B-O	Observed number	Observed per cent	Expected number	Expected per cent
O	17	47.22	16.79	46.64
A_1	11	30.55	10.53	29.25
A_2	5	13.89	5.68	15.77
B	2	5.56	2.16	6.00
A_1B	0	0.00	0.51	1.42
A_2B	1	2.78	0.33	0.92
Total	36	100.00	36.00	100.00
x^2		0.769 with 2 D.F.		
M–N				
M	6	16.67	7.11	19.75
MN	20	55.56	17.78	49.39
N	10	27.78	11.11	30.86
Total	36	100.01	36.00	100.00
x^2		0.5614 with 1 D.F.		

Gene frequencies

(1)		(2)	
r	.6830±.0602	m	.4445±.0586
p_1	.1674±.0474	n	.5555±.0586
p_2	.1071±.0413		
q	.0425±.0240		
Total	1.0000		1.0000

1. Maximum likelihood method of *Stevens* [1938].
2. Gene counting method of *Boyd* [1950], p. 395.

Table 8. A–B–O and M–N blood groups of fourth generation individuals in the Shoshone, Idaho, sample

Blood Group System A-B-O	Observed number	Observed per cent	Expected number	Expected per cent
O	22	44.00	21.03	42.06
A_1	15	30.00	14.55	29.10
A_2	10	20.00	11.45	22.90
B	1	2.00	2.00	4.00
A_1B	0	0.00	0.49	0.98
A_2B	2	4.00	0.48	0.94
Total	50	100.00	50.00	99.98
x^2		0.1984 with 2 D.F.		
M–N				
M	9	18.00	10.58	21.16
MN	28	56.00	24.84	49.68
N	13	26.00	14.58	29.16
Total	50	100.00	50.00	100.00
x^2		0.8092 with 1 D.F.		
		Gene frequencies		
(1)			(2)	
r	.6486±.0525		m	.4600±.0498
p_1	.1638±.0365		n	.5400±.0498
p_2	.1574±.0406			
q	.0302±.0188			
Total	1.0000			1.0000

1. Maximum likelihood method of *Stevens* [1938].
2. Gene counting method of *Boyd* [1950], p. 395.

can not be distinguished from a more transitory fluctuation where data on only two generations are available. A continuation of the differences in the magnitude seen here would of course be of considerable importance.

Excess of MN

It has been observed that there is often an excess of MN children from MN × MN matings where the expected ratio is 1 M : 2 MN : 1 N. Various explanations have been offered attributing this excess to technical errors or to

survival selection in favor of the heterozygote (*Wiener* [1943, p. 236–242 and 1951], *Taylor* and *Prior* [1938], *Race* and *Sanger* [1950]).

In our material it is possible to check for technical errors in four of the five kinds of matings, or in 78 out of the 117 individuals involved.

Table 9. Rh blood types in third generation individuals in the Shoshone, Idaho, sample

Most Probable Genotype *Fisher*	Genotype *Wiener*	Observed number	Observed per cent	Expected[1] number	Expected[1] per cent
cde/cde	rr	8	22.22	7.11	19.75
CDe/cde	R_1r	7	19.44	7.08	19.67
CDe/Cde	R_1r'	6	16.67	4.65	12.92
Cde/cde	r′r	7	19.44	5.81	16.14
Cde/Cde	r′r′	0	0.00	1.19	3.31
cDe/cde	R_2r	0	0.00	0.00	0.00
cDE/cde	R_2r	1	2.78	4.15	11.53
cDE/cDE	R_2R_2	3	8.33	1.07	2.97
CDe/cDE	R_1R_2	3	8.33	4.23	11.75
cdE/cde	r″r	1	2.78	0.50	1.39
CDE/Cde	R_2r'	0	0.00	0.00	0.00
CdE/cde	r_yr	0	0.00	0.20	0.56
Total		36	99.99	35.99	99.99

Gene frequencies[2]

cde–r	.4444
CDe–R_1	.2213
Cde–r′	.1815
CDE–R_z	.0000
cDE–R_2	.1373
cdE–r″	.0155
cDe–R_0	.0000
Total	1.0000

$x^2 = 0.8206$ with 2 D.F.

[1] *Boyd, W. C.* [1954].

[2] *Mourant, A. E.* [1954], p. 224–232.

No errors are detectable in the 48 children of the first four kinds of mating. The expected numbers for the MN × MN matings are 5.75 M : 11.50 MN : 5.75 N. A chi-square test nevertheless gives a value of 5.2608 with one degree of freedom, significant at the 5 % level.

Kind of Mating	Number	Offspring M	Offspring MN	Offspring N	Total Children
M × N	2	0	0	8	8
MN × M	7	12	11	0	23
MN × N	5	0	10	5	15
M × N	1	0	2	0	2
MN × MN	8	7	15	1	23
	23	19	38	14	71
	(= 46 parents)				

Table 10. Rh blood types in fourth generation individuals in the Shoshone, Idaho, sample

Most Probable Genotype *Fisher*	Genotype *Wiener*	Observed number	Observed per cent	Expected [1] number	Expected [1] per cent
cde/cde	rr	6	12.00	7.49	14.98
CDe/cde	R_1r	7	14.00	5.00	10.00
CDe/Cde	R_1r'	6	12.00	3.64	7.28
Cde/cde	$r'r$	15	30.00	13.06	26.12
Cde/Cde	$r'r'$	3	6.00	5.69	11.38
cDe/cde	R_0r	1	2.00	1.25	2.50
cDE/cde	R_2r	5	10.00	4.59	9.18
cDE/cDE	R_2R_2	3	6.00	1.25	2.50
CDe/cDE	R_1R_2	2	4.00	6.78	13.50
cdE/cde	$r''r$	0	0.00	0.00	0.00
CDE/Cde	R_zr'	2	4.00	1.25	2.50
CdE/cde	r_yr	0	0.00	0.00	0.00
Total		50	100.00	50.00	100.00

Gene frequencies [2]

cde–r	.3870
CDe–R_1	.0946
Cde–r'	.3373
CDE–R_z	.0281
cDE–R_2	.1219
cdE–r''	.0000
cDe–R_0	.0311
Total	1.0000

$x^2 = 8.1298$ with 4 D.F. [3]

[1] *Boyd, W. C.* [1954].
[2] *Mourant, A. E.* [1954], p. 224–232.
[3] *Beteeen, P.* $_{05}$ and P. $_{10}$.

Rh Type and Number of Children

Although the numbers involved are very small it is worth while to inspect the Rh type of mothers and the number of children. As the following table indicates, the mothers who are cde/cde (rr) have slightly fewer living children but no significance can be attributed to this difference in view of the small number.

Rh Type of Mother	Number	Number of Stillbirths	Number of Miscarriages	Total	Living Children
cde/cde (rr)	13	1	11	12	42
CDe/--- (R_1--)	10	3	1	4	36

Owing to the fact that the information concerning stillbirths and miscarriages depended upon the memory of the persons involved it does not bear the same kind of validity as the number of living children. It could, of course, be enormously important, especially the high frequency of reported miscarriages among the Rh negative mothers.

Comments

The isolates described her present certain unique aspects. The Shoshone isolate displays an interestingly low frequency of R_1r (CDe/cde) when compared with other Basques series. The frequency for the Boise isolate is higher, but still lower than for most Basque series.

As a consequence of the high degree of relatedness inside the Shoshone isolate an increasingly larger proportion of mates must be drawn from non-Basque populations. This presumes that the other alternatives such as abandonment of the rules concerning the mating of first cousins, the cessation of marriage or the arrival of a great many more Basques, are highly improbable.

Hemolytic disease of the newborn also serves to promote the introduction of non-Basque genes in this isolate. Thus, a woman who is unable to bear her own children, owing to Rh sensitization, adopts children who are not Basque.

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Discussion

J. V. Neel (Ann Arbor): You have called attention to a point which has recurred several times in the litterature, the excess of MN children in MN × MN matings. Do you have any explanation for this?

W. S. Laughlin (Wisconsin): We have no explanation for this significant excess of MN. We do feel that it can not be explained by technical error in view of the genealogical checks referred to and in view of the extreme care used in searching for sources of error. Thus, it appears that we may give attention to the possibility of selection for the heterozygote.

Ph. Levine (Raritan, New Jersey): To Dr. *Kalmus:* I apologize to Dr. *Kalmus* because of my comments on the small sample of Brazilian Indians tested for Diego. Certainly the high incidence of Diego positive reaction in these and other Americ-indians, and somewhat lower values in Chinese and Japanese is well established. With regard to the second case of anti-Di^a this occurred in a Polish family (both man and wife) and *Lewis, Chown* and *Levine* suggest that this may be due to some Mongolian elements in a Polish population.

To Dr. *Laughlin:* I am somewhat disturbed by the the high incidence of r′ (dCe) chromosome in the third generation of his Basque population of Idaho. In view of the findings of *Ceppelini* and *Danos* on the influence of r′ on the chromosome containing D as in the combinations of DCe dCe(R^1r'), one should expect a high incidence of D^u reactions. If missed by virtue of weak reactivity, this could result in higher values for chromosomes r(dce).

A. E. Mourant (London): With regard to Dr. *Laughlin*'s communication I am most interested in the fall in Rh-negative incidence in American-born Basques though it would be highly premature and perhaps even unrealistic to attribute the effect or even a large part of it to the *geographical environment.*

I should like to know what tests were used by Dr. *Vijenhuis* when searching for the D^u antigene. I realize that adequate tests by present standards were not done on my own series of Basques.

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ASSOCIATIONS BETWEEN BLOOD GROUPS AND DISEASE

By J. A. FRASER ROBERTS*

There must be many people who recall, and not without some feelings of guilt, how, 20 years ago, you, Mr. *Chairman*** and Dr. *Ford*, urged, indeed implored, those who had the facilities to look for associations between blood-groups and adult diseases. I had little access to suitable material in those days, but I share the feelings of guilt, because I remember saying to Dr. *Ford* that I thought it would be more profitable to start with maternity and children's hospitals and look for selective elimination in prenatal and early life.

It is true that work had been done, though usually on too small a scale. I will not go into these early researches, except just to mention that *Buchanan* and *Higley* in 1921 had actually found the association between group O and peptic ulceration. This, however, is in retrospect. Their own statement was: "There is no relationship between blood-groups and any disease in which sufficient data are available to justify a conclusion." Much later, *Ugelli* in 1936 made the same observation and drew the right deduction. I must also mention the valuable work of Professor *Moureau* who, in particular, refuted the erroneous idea that diseases could change the blood-groups. Coming to more recent times there is the very important observation of *Struthers* on bronchopneumonia already mentioned by Dr. *Mourant*.

The crux of the whole problem is, of course, numbers. To detect even very large associations we need series amounting to thousands rather than hundreds; and it is only three years ago that a really large number, more than 3,000, was collected for a single disease entity. This effort was due to the wholly admirable pertinacity of my friend Professor *Aird*. Overcoming

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all difficulties he arranged for the collection of data on cancer of the stomach from a large number of different hospitals. Professor *Aird* had a hypothesis to test. The hypothesis proved to be wrong, but the result was magnificent. It was a perfectly reasonable hypothesis and well worth testing; but, as happens not infrequently, what turned up was something different and even more interesting: in fact, just what you, Mr. *Chairman*, and Dr. *Ford*, had been waiting for, for so long.

It is a remarkable piece of luck that when a really large sample was collected for the first time a positive result should have been obtained. It could so easily have happened that the first, the second, a number, of negative results would have followed each other: then everyone would probably have become discouraged. As it is, of course, progress has been rapid. Had I been reading this paper a month ago one important conclusion would have been different. And I am sure that we are going to hear of new and interesting developments at this conference.

Table 1. Duodenal ulcer. 8 centres

Group	Ulcer NO.	Ulcer %	Corresponding Controls weighted %
O	3,948	55.51	47.32
A	2,423	34.07	39.81
B	564	7.93	9.60
AB	177	2.49	3.27
Total	7,112		

Relative incidence of disease

In Persons of Group:	Compared with Persons of Group:	Relative Incidence
O	A	1.37
O	B	1.42
O	AB	1.54
A	B	1.04
A	AB	1.12
B	AB	1.08

Starting with duodenal ulcer, here are the results up to date, as far as they are known to me. In this preliminary table they are shown in brief summary form, combining the series from 8 centres and comparing them with suitably weighted controls. What emerges on more detailed analysis

is just what would be deduced from inspection of these figures. The incidence of duodenal ulcer in persons of group O is substantially raised as against its incidence in all the other ABO groups. Even the difference between O and AB is highly significant. Between themselves groups A, B and AB show no significant differences. This determines the most useful simple analysis, which is shown in table 2.

Table 2. Duodenal ulcer

	Centre	Ulcer O	Ulcer A+B+AB	Controls O	Controls A+B+AB	Relative Incidence in Group O	χ^2
1.	London	535	411	4,578	5,422	1.54	39.83
2.	Manchester	225	198	4,532	4,338	1.21	3.76
3.	Newcastle	288	194	6,598	6,974	1.57	22.75
4.	Liverpool	631	428	7,527	7,850	1.54	44.26
5.	Glasgow	947	695	3,177	2,721	1.17	7.51
6.	Copenhagen	342	338	5,804	8,500	1.48	25.06
7.	Oslo	282	297	3,135	5,157	1.56	26.77
8.	Iowa	698	603	2,892	3,421	1.37	26.49
		3,948	3,164	38,243	44,883		196.425

X = combined weighted mean incidence in Group O relative to the others = 1.40. Approximate 95% fiducial limits of X, 1. 33–1. 47.

	D. of F.	χ^2	p.
Difference from unity	1	176.13	
Heterogeneity	7	20.30	.005
Total	8	196.43	

1–3, *Aird* et al.; 4, *Clarke* et al.; 5, *Brown* et al.; 6, *Køster* et al.; 7, *Heistö;* 8, *Buckwalter* et al.

Here we compare the incidence of duodenal ulcer in persons of group O relative to its incidence in persons of the other groups added together. The method used is a very useful development due to Dr. *Woolf.* With diseases it seems natural to work in terms of incidences, and this is what *Woolf*'s method does. The results thus come out in a form with a direct and simple meaning. Furthermore, series can be added from areas with very different gene frequencies in their populations.

Combining the 7,000 cases collected at the 8 centres the incidence of the disease in persons of group O is 140 as against 100 in persons of groups A, B and AB. The 95 per cent fiducial limits are quite narrow, 133 and 147. It should be mentioned that these limits depend on large sample treatment and are approximate.

All areas, from Oslo to Iowa, show the increased incidence, but there is highly significant heterogeneity. Up to a month ago the published series were homogeneous, but now the Glasgow sample has been added, the largest so far collected from a single centre. At Glasgow the relative incidence is down to 1.17, which has raised the χ^2 for heterogeneity to 20 for 7 degrees of freedom, corresponding to a probability of 1 in 200. There does not appear to be any obvious immediate explanation for the low figure at Glasgow. True, Glasgow has the highest frequency of gene O, but Newcastle, not much lower in O, shows the highest relative incidence of any centre. It is perhaps to be expected that when series are collected from many places and numbers become really large, heterogeneity should appear, and it may well provide clues and indications for further work. Clearly, it would be very useful to have data from many more centres, especially, of course, from countries with quite different gene frequencies, like India and Japan.

Table 3. Gastric ulcer

	Centre	Ulcer O	Ulcer A–B–AB	Controls O	Controls A–B–AB	Relative Incidence in Group O	χ^2
1.	London	314	285	4.578	5.422	1.30	9.98
2.	Manchester	122	110	4.532	4.838	1.18	1.61
3.	Newcastle	102	82	6.598	6.974	1.31	3.36
4.	Liverpool	215	223	7.527	7.850	1.01	0.00
5.	Glasgow	174	126	3.177	2.721	1.18	1.96
6.	Copenhagen	156	181	5.804	8.500	1.26	3.66
7.	Oslo	179	233	3,135	5,157	1.26	5.27
8.	Iowa	248	221	2.892	3.421	1.33	8.73
		1.510	1.461	38.243	44.883		34.57

X = 1.23 95% Fiducial limits, 1.14–1.32

	D. of F.	χ^2	p.
Difference from unity	1	28.62	
Heterogeneity	7	5.94	.55

1–3, *Aird* et al.; 4, *Clarke* et al.; 5, *Brown* et al.; 6, *Køster* et al.; 7, *Westlund* and *Heistö*; 8, *Buckwalter* et al.

Turning to gastric ulcer at the same 8 centres, the relative incidence in persons of group O is 1.23, and here the series are so far perfectly homogeneous, though, of course, the numbers are considerably smaller. We may note that even with an overall 23 per cent excess there is nothing especially odd about getting an entirely negative result from a sample of more than 400, as at Liverpool. It is a clear indication of the need for large numbers.

Table 4. Duodenal ulcer compared with gastric ulcer

	Centre	Ulcer O	Ulcer A+B+AB	Controls O	Controls A+B+AB	Relative Incidence in Group O	χ^2
1.	London	535	411	314	285	1.18	2.53
2.	Manchester	225	198	122	110	1.02	0.02
3.	Newcastle	228	194	102	82	1.19	1.02
4.	Liverpool	631	428	215	223	1.53	13.82
5.	Glasgow	947	695	174	126	0.99	0.01
6.	Copenhagen	342	338	156	181	1.17	1.44
7.	Oslo	282	297	179	233	1.24	2.67
8.	Iowa	698	603	248	221	1.03	0.08
		3,948	3,164	1,510	1,461		21.59

X = 1.17, 95% Fiducial limits, 1.07–1.28

	D. of F.	χ^2	p.
Difference from unity	1	12.09	.0005
Heterogeneity	7	9.50	.22

1–3, *Aird* et al.; 4, *Clarke* et al.; 5, *Brown* et al.; 6, *Køster* et al.; 7, *Westlund* and *Heistö;* 8, *Buckwalter* et al.

The relative incidence is increased in gastric ulcer with very high significance, but it is a lower figure than in duodenal ulcer. Table 4 shows a direct comparison of duodenal and gastric ulcer. What we now look at is increased incidence in group O of duodenal ulcer over and above the lesser increase in gastric ulcer. In our original data for London, Manchester and Newcastle the difference was not significant, which was why we made most comparisons in terms of peptic ulcer. Then came results from Oslo and from Liverpool, which made it significant. χ^2 for the difference has fluctuated considerably as new series have appeared. It reached a high figure, but now the Glasgow series has brought it down again to 12. No doubt the evidence for a difference is strong, but it can hardly be called overwhelming. On these numbers there is no evidence that the 8 areas are heterogeneous for the difference.

Table 5 shows the results for carcinoma of the stomach at 10 centres. The comparison shown is the relative incidence of the disease in persons of group A, compared with that in persons of group O. The figure is 1.23. Here once again the areas are homogeneous.

Some figures in a letter from Japan were quoted in a paper read at the 5th Meeting of the International Society of Geographical Pathology in 1954. I have only just seen this reference. Dr. *Kurokawa*, the writer of the letter, stated that there is an excess of A and a deficiency of AB. The number of

Table 5. Carcinoma of stomach

	Centre	Carcinoma O	Carcinoma A	Controls O	Controls A	Relative Incidence in Group A	χ^2
1.	London	578	617	4,578	4,219	1.16	5.67
2.	Manchester	343	349	4,532	3,775	1.22	6.39
3.	Newcastle	44	44	6,598	5,261	1.25	1.12
4.	Liverpool	85	97	462	402	1.31	2.75
5.	Birmingham	37	57	458	442	1.60	4.46
6.	Leeds	92	104	11,359	9,805	1.31	3.52
7.	Glasgow	159	104	3,853	2,485	1.01	0.01
8.	Basle	255	374	1,882	2,036	1.36	12.16
9.	Copenhagen	141	212	5,804	6,299	1.39	8.75
10.	Iowa	370	403	2,892	2,625	1.20	5.62
		2,104	2,361	42,418	37,349		

X = 1.23, 95% Fiducial limits, 1.15–1.31

	D. of F.	χ^2	p.
Difference from unity	7	43.01	
Heterogeneity	9	7.45	.6

1–6, *Aird* et al.; 7, *Wallace;* 8, *Hollander;* 9, *Køster* et al.; 10, *Buckwalter* et al.

cases is only 256, however, and comparing them with the general Japanese ABO frequencies (no control figures are quoted) the differences are small. It would be extremely interesting to get more results from Japan. Possibly someone at this Meeting may know of further work.

Now it would be suspicious and disturbing if all diseases were to show positive associations. Negative results are often very welcome, especially in

Table 6. Carcinoma of bronchus

	Centre	Carcinoma O	Carcinoma A	Controls O	Controls A	Relative Incidence in Group A	χ^2
1.	London	166	162	4,578	4,219	1.06	0.26
2.	Birmingham	128	110	458	442	0.89	0.63
3.	Manchester .	160	140	4,532	3,775	1.05	0.17
4.	Liverpool	458	377	2,807	2,428	0.95	0.44
		912	789	12,375	10,864		1.50

X = 0.98, 95% Fiducial limits, 0.89–1.09

	D. of F.	χ^2	p.
Difference from unity	1	0.10	.9
Heterogeneity	3	1.40	.7

1–3, *Aird* et al.; 4, *Clarke* et al.

a new field where we are feeling our way. Moreover, negative results from the same centres and hospitals are an excellent second-line control when positive results have been obtained for other diseases. Here is one negative result: for carcinoma of the bronchus. The comparison is A versus O, the incidence in the two groups being practically the same. The number in the disease series, however, is only 1,700 and so the approximate 95 % fiducial limits are fairly wide. An association might turn up with larger numbers, and it would be well worth while collecting more figures. For the moment, however, the result is entirely negative, and the areas are perfectly homogeneous. Negative results have been found with ABO and cancer of the breast, though the numbers are rather small. There are also negative results for ABO and hypertension, though here there is a possibly suggestive deficiency of AB's in the men. We can now add toxaemia of pregnancy to the negative results. The original finding of an association with O has been negatived by a further series from the same hospital, as well as by large series from another hospital.

Table 7. Carcinoma of colon and rectum

	Centre	Carcinoma O	Carcinoma A	Controls O	Controls A	Relative Incidence in Group A	χ^2
1.	London	665	676	4,578	4,219	1.10	2.80
2.	Manchester	163	152	4,532	3,775	1.12	0.97
3.	Newcastle	99	79	6,598	5,261	1.00	0.00
4.	Birmingham	237	227	458	442	0.99	0.00
		1,164	1,134	16,166	13,697		3.77

X = 1.08, 95% Fiducial limits, 0.99–1.18

	D. of F.	χ^2	p.
Difference from unity	1	2.74	.1
Heterogeneity	3	1.03	.8

1–4, *Aird* et al.

Here is another negative result—for cancer of the colon and rectum. In view, however, of the fact that the associations discovered so far are so much concerned with gastro-intestinal and related diseases, and that there is an excess, though non-significant, of cancer of the colon and rectum in group A, it is very desirable that further series should be collected. A number not less than, say, 2,000 would probably be needed, however.

The discovery of large associations has prompted forward studies, which have so far produced two more positive results. Here is one of them.

Table 8. Diabetes mellitus

		Diabetes A+AB	Diabetes O+B	Controls A+AB	Controls O+B	Relative Incidence in Groups A+AB	χ^2
Men	1. S.W. Lancashire	111	110	2,818	3,692	1.32	4.16
	2. W. Cheshire	47	35	566	681	1.62	4.34
	3. Oxford	97	84	3,047	3,445	1.31	3.11
	4. Glasgow	101	174	2,748	4,670	0.99	0.01
		356	403	9,179	12,488		11.62
Women	1. S.W. Lancashire	182	231	2,818	3,692	1.03	0.10
	2. W. Cheshire	55	62	566	681	1.07	0.11
	3. Oxford	159	160	3,047	3,445	1.12	1.03
	4. Glasgow	224	317	2,748	4,670	1.20	4.09
		620	770	9,179	12,488		5.33

X = Men, 1.21; women, 1.12.

	D. of F.	Men v. χ^2	Con. p.	Women v. χ^2	Con, p.	Men v. χ^2	Women p.
Difference from unity	1	6.81	.009	4.04	.045	0.78	.4
Heterogeneity	3	4.81	.19	1.29	.7	5.77	.12

1-3, *McConnell* et al.; 4, *Craig* and *Wang*.

Dr. *McConnell* at Liverpool and Dr. *Pyke* at Oxford independently found an excess of A in diabetes mellitus. The comparison shown in the slide is persons with gene A, namely A plus AB, against persons without it, O and B. I show these because we have done most computing with this comparison: but the results are much the same if A and O are taken alone. Analysis showed that the excess was in men, the excess in women being non-significant and very small. Direct comparison of the sexes gave a χ^2 of 4.3 for one degree of freedom, so that there was some evidence for a real sex difference. But now comes the series of Dr. *Craig* and Dr. *Wang* at Glasgow, showing no difference in the men, but a difference just significant on this series alone in the women. Pooling all the figures, the difference in the men is significant, though lowered; the difference is also significant in the women; and there is no significant heterogeneity of areas. Turning to the last figures in the table, the evidence for a sex difference has disappeared. χ^2 for the sex difference is now only .8, and for heterogeneity of areas for the sex difference 5.8, which for 3 degrees of freedom corresponds to a P. of .12. So now we can substitute for the original rather complicated story the straight comparison shown in the next table.

Table 9. Diabetes mellitus — Sexes combined

	Diabetes A+AB	Diabetes O+B	Controls A+AB	Controls O+B	Relative Incidence in Groups A+AB	χ^2
1. S.W. Lancashire	293	341	2,818	3,692	1.13	2.01
2. W. Cheshire	102	97	566	681	1.27	2.37
3. Oxford	256	244	3,047	3,445	1.19	3.38
4. Glasgow	325	491	2,748	4,670	1.12	2.43
	976	1,173	9,179	12,488		10.20

X = 1.15, 95% Fiducial limits, 1.05–1.26.

	D. of F.	χ^2	p.
Difference from unity	1	9.55	.002
Heterogeneity	3	0.65	.89

1–3, *McConnell* et al.; 4, *Craig* and *Wang*.

There is quite good evidence—a P. of 1 in 500—that diabetes is commoner in persons with gene A, and the 4 areas are not significantly heterogeneous. The figure for relative incidence is 1.15. But of course we are dealing with an altogether lower order of likelihood than with peptic ulcer and cancer of the stomach. Many more figures are needed.

You will, be hearing in a later paper by Mr. *Bentall* about a second positive result produced by a forward study. The pooled results of a number of workers in Great Britain show an association between group A and pernicious anaemia, the probability being of the same order as that just given for diabetes mellitus.

We have, then, overwhelming evidence for associations with three diseases, duodenal ulcer, gastric ulcer and carcinoma of the stomach, and quite strong evidence for two more, diabetes mellitus and pernicious anaemia. In two of them persons of group O are at a disadvantage; in three persons of group A. It is rather remarkable, perhaps, to find that in all five diseases persons of group B go with the favoured group. So we have yet to discover what it is that people of group B suffer from. No doubt it will emerge in time.

I will keep this summary slide on the screen while I make a few concluding remarks. The slide does not include pernicious anaemia.

So far I have dealt only with ABO. Series have been collected for Rhesus, D-positive and negative only. The numbers are large for some diseases, especially peptic ulcer, and the results so far are negative. In my opinion, and as far as I know the literature, there is no satisfactory evidence

Table 10. Summary table

Disease	No. in Disease Series	Relative Incidence in Groups:	Relative Incidence Groups:	Wgtd. Mean Incidence	95% Fiducial Limits
Duodenal Ulcer	7,112	O	A+B+AB	1.40	1.33—1.47
Gastric Ulcer	2,971	O	A+B+AB	1.23	1.14—1.32
Carcinoma of Stomach . . .	4,465	A	O	1.23	1.16—1.31
Diabetes mellitus	2,149	A+AB	O+B	1.15	1.05—1.26
Carcinoma of Colon and Rectum	2,599	A	O	1.08	0.99—1.18
Carcinoma of Bronchus . . .	1,701	A	O	0.98	0.89—1.09
Carcinoma of Breast	1,017	A	O	1.02	0.88—1.18
Toxaemia of Pregnancy . . .	1,385	O	A	0.98	0.87—1.11
Hypertension	2,147	O	A	1.02	0.91—1.13

for associations between Rhesus and disease—other, needless to say, than haemolytic disease. I know that some claims have been made, but I will not mention them. It would be ungracious to refer to such work unless one could also give in detail one's reasons for doubting the conclusions, and there is no time for this.

In this subject we see biometry, some to-day might use the word epidemiology, performing one of its traditional services: first, of discovering problems to be investigated; secondly, of establishing ancillary findings which must be accommodated in any hypothesis, and which help in directing researches along promising lines. A major phenomenon has been revealed, though not much can be said yet about the mechanisms which underlie it. We cannot yet even exclude the possibility, though it seems unlikely, that the associations are not directly causal, but are due to stratification in the population. Anyway a wide field for diverse researches has been opened up and we shall, I hope, be hearing some of the results at this conference.

There are still great opportunities for further work at the preliminary biometric level. A search can be made for associations with many other diseases. We also want more data on those already investigated, even where the numbers are largest. Particularly, of course, we need data from new centres, and above all from regions of quite different blood-group frequencies from those of Western Europe and North America.

The ancillary observations depend chiefly on subdivision, which calls for even vaster numbers. Sex and age are obvious as a first choice. Here I am afraid we set a bad example in the original paper on cancer of the stomach. But there was an excuse. The hospitals were doing the work them-

selves and Professor *Aird* wisely decided that in this trial effort the particulars asked for should be kept to an absolute minimum—though he did regret later not asking at least for sex. But it should not happen again. In the results so far available no clear differences due to sex have in fact emerged, now that the story of diabetes mellitus has become rationalized. But negative findings, too, may be important. It is noteworthy that in duodenal ulcer, with its very different incidence in the two sexes, the increased incidence in group O should be the same in both. No clear age associations either have appeared up to the present. Even in diabetes mellitus, where it is especially natural to look for age differences, the figures, even under extreme torture, refused to reveal anything. But we must go on looking: age and sex differences are sure to turn up sometime.

Here I must say a word of mild protest. Dr. *Køster* and his colleagues, in their very interesting paper on peptic ulcer and cancer of the stomach, did not give age and sex breakdowns, not because they did not have them, but because they had no corresponding breakdowns for the control donor panel. Now many, many studies have been carried out on sex and age distributions in donor material, amounting in the aggregate to many hundreds of thousands. Invariably there has either been no difference at all, or very small differences—very small, that is, in the present context. It is surely legitimate to break down disease series by age and sex, at the same time using total undivided controls. If, some day, we find 5 per cent sex or age differences in a donor panel, we shall be very sorry if misleading conclusions have been drawn; but we shall also be exceedingly surprised.

There are many other useful subdivisions that can be made: the most important being subdivision of the disease. The difference between the related diseases, gastric and duodenal ulcer, is a beginning, and you will be hearing something more from Mr. *Bentall.*

Finally, turning to the planning of the work, there are three levels at which we can look for data. First, and easiest, are retrospective studies on hospital records of diseases in which blood-grouping tends to be done as a routine. Most of these possibilities have been exploited already, but we can do with larger numbers. At this level we are limited to two blood-group systems, ABO and Rhesus, D-positive and negative only. The next stage is forward studies on diseases common enough to yield large numbers in a relatively short time. Here, too, shortage of sera, and of workers to use them, limit the work to ABO and Rhesus. Of course, all the blood-groups are potentially of equal value and the third stage, detailed simultaneous studies on as many as possible, combined with family studies, would be the best thing of all. It is greatly to be hoped that this larger work will be under-

taken; but, of course, it involves really long term planning and it will take many years before adequate numbers can be accumulated. In perceiving, however, what would be ideal, we should not neglect the useful work still to be done at the simpler levels, with their opportunities for securing large numbers in a short time. To use a favourite quotation of my old friend *Major Greenwood:* "Don't make the best the enemy of the good".

Everything is in favour of a rapid increase in knowledge. On the one hand there are the vast operations of the blood transfusion services, and on the other the chance of opening up new methods of research on important diseases, should the associations prove to be causal, and this seems likely. It is practical requirements which have ensured that for more than a quarter of a century more would always be known about geographical variations in the frequencies of the human blood-group genes than about any other genes, plant or animal. The same factors should now ensure another important contribution to the understanding of the workings of natural selection.

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DISEASE ASSOCIATIONS OF THE ABO BLOOD GROUP

By J. A. BUCKWALTER

In reporting the results of earlier investigations done in the United States, the authors concluded there was no convincing evidence of an association between the ABO blood groups and the diseases studied, although on examining the data collected by *Buchanan* and *Higley* in 1920, there was indication of an association for peptic ulcer. A project was designed to explore the possibility of such associations in the population of the State of Iowa. Data was obtained by review of more than 20,000 case records from the University and five other Iowa hospitals. Information regarding blood type and rigorous diagnostic criteria were the only two factors acting to select cases. Histologic diagnoses were required for the neoplasms and surgical or "iron clad" clinical diagnoses for the other disorders. The data were evaluated by comparing the observed blood type frequencies with those of some 6,000 blood donors who were the controls for this study. The statistical significance of the differences in blood type frequencies occurring between the patients and controls was examined by the Chi Square and difference in percentage methods. In examining the data, the eleven possible combinations and comparisons were made. The results of the O:A:B:AB and O:A comparisons are reported since they are most pertinent to the findings. The data are recorded in table 1.

The search for possible secondary associations included Rh blood type, age, sex, method of diagnosis and treatment. No statistical significance was found for the differences occurring between these subgroups of patients for any of the disorders. A decrease in the Rh negative percentage in patients with carcinoma of the lung although not statistically significant, was of interest in view of similar data previously reported. In peptic ulcer the

Table 1. Basic data: Patients, controls and probabilities when Chi Square is calculated for O:A:B:AB and O:A comparisons

Patients	Blood types				Patients vs. controls probability	
	O	A	B	AB	O:A:B:AB	O:A
Peptic ulcer	983	679	134	43		
1839	(53.5%)	(36.9%)	(7.3%)	(2.3%)	$P < .001$	$P < .001$
Duodenal	698	472	102	29		
1301	(53.7%)	(36.3%)	(7.8%)	(2.2%)	$P < .001$	$P < .001$
Gastric	248	183	26	12		
469	(52.9%)	(39.0%)	(5.5%)	(2.6%)	$.001 < P < .01$	$.02 < P < .05$
Both	37	24	6	2		
69	(53.6)	(34.8%)	(8.7%)	(2.9%)	$.10 < P$	$.10 < P$
Gastric carcinoma	383	416	84	25		
908	(42.2%)	(45.8%)	(9.2%)	(2.8%)	$.05 < P < .10$	$.01 < P < .02$
Pernicious anemia	59	76	14	9		
158	(37.3%)	(48.1%)	(8.9%)	(5.7%)	$.05 < P < .10$	$.02 < P < .05$
Breast carcinoma	370	383	81	32		
866	(42.7%)	(44.2%)	(9.4%)	(3.7%)	$.10 < P$	$.05 < P < .10$
Lung carcinoma	202	144	33	16		
395	(51.1%)	(36.5%)	(8.4%)	(4.0%)	$.10 < P$	$.02 < P < .05$
Rheumatic disease	100	113	26	15		
254	(39.4%)	(44.5%)	(10.2%)	(5.9%)	$.05 < P < .10$	$.10 < P$
Hip fractures	382	408	90	30		
910	(42.0%)	(44.8%)	(9.9%)	(3.3%)	$.10 < P$	$.02 < P < .05$
Controls	2892	2625	570	226		
6313	(45.8%)	(41.6%)	(9.0%)	(3.6%)		

association appears to be strongest in patients with high levels of free HCl acid; this is supported by the statistically significant difference noted when patients with a marked increase and no increase in free HCl acid after histamine are compared.

When Chi Square is calculated for the O:A:AB comparison of patients with rheumatic disease, we obtain $.02 < P < .05$, or a higher level of significance than indicated by the two comparisons recorded in table 1. This is in keeping with the possibility that blood types A and AB may be implicated in the genesis of these diseases, suggested by the observations concerning A blood group substance and its relationship to streptococcal antigenic properties.

The following assertions are warranted by the data presented with regard to the association of the ABO blood groups and disease. A highly significant association exists for peptic ulcer, not differing significantly for duodenal and gastric ulcer. A significant association for gastric carcinoma and a probably significant association for pernicious anemia have been observed. More data must be collected before the findings in breast and lung cancer can be properly interpreted. It is probable in view of previous studies indicating no associations for these diseases, that the additional data will result in the disappearance of the equivocal evidence of significance. With regard to rheumatic disease and fractured hips, there is a similar need for more data.

More data are needed for clearer definition of these and other possible associations. Rigorous diagnostic criteria must be employed to insure maximum homogeneity of patient groups. There is need for continuing attention to the question of validity of the controls. Proper methods of statistical analysis must be used. Obviously at this time it is impossible to predict with any certainty the ultimate pattern of these associations which will emerge as the results of investigations now in progress accumulate. However, the possibility of a dynamically balanced set of selective factors controlling the gene formula within the observed limits, linked to the blood groups, is suggested.

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ÉTUDE DE RELATION DES GROUPES SANGUINS (ABO) ET RHÉSUS (STANDARD) DANS LE DIABÈTE

Prédominance de Groupe (A) dans Certaines Complications du Diabète (Rapport préliminaire) [1]

Par I. ZEYTINOGLU

Nous avons étudié chez les diabétiques (x) les groupes sanguins ABO et le facteur Rhésus (standard). Les examens ont porté sur 432 diabétiques (n).

Le résultat a été le suivant:

a) La répartition des groupes sanguins ABO chez les diabétiques était très comparable à celle notée chez les sujets de contrôle (tableau 1).

Tableau 1. Répartition globale des groupes sanguins chez les diabétiques et chez les sujets de contrôle

Groupe sanguin	Contrôle [1] Nombre	Contrôle [1] %	Diabétiques Nombre	Diabétiques %
A	11 303	47,2	201	46,5
B	1 951	8,2	48	11,1
O	9 686	41,0	167	38,6
AB	850	3,6	16	3,7
Total	23 790		432	

[1] Statistique de Dr *R. Fischer* (Directeur du Centre de transfusion de l'Hôpital Cantonal de Genève).

[1] Cette étude est faite à la Clinique Médicale Universitaire de Genève, du Prof. *G. Bickel*, ce dont je lui suis très reconnaissant.

[2] Grâce a l'amabilité du Prof. *R. S. Mach* (Clinique Thérapeutique) et du Prof. *E. Martin* (Policlinique Médicale) nous avons pu consulter une partie de leurs dossiers.

b) La répartition de groupe Rh (standard) a donnée des résultats superposables chez les diabétiques et chez les sujets de contrôle (tableau 2).

Tableau 2. Répartition de Rh standard chez les diabétiques et chez les sujets de contrôle

Rhésus	Contrôle [1] Nombre	Contrôle [1] %	Diabétiques Nombre	Diabétiques %
Rh+	19 695	82,8	355	82,1
Rh—	4 095	17,2	77	17,1
Total	23 790		432	

[1] Statistique de *R. Fischer*.

c) Parmi nos 432 diabétiques, 39 développèrent un syndrome de *Kimmelstiel-Wilson* et nous avons été frappés de constater que parmi ces derniers, 31 étaient du groupe (A), qui était ainsi représenté dans la très forte proportion de 79,4 pour cent (tableau 3).

Tableau 3. Répartition des groupes sanguins, chez les diabétiques simples et le Kimmelstiel-Wilson

Groupe sanguin	Diabète Simple Nombre	Diabète Simple %	*Kimmelstiel-Wilson* Nombre	*Kimmelstiel-Wilson* %
A	170	43,2	31	79,4
B	46	11,7	2	5,1
O	162	41,2	5	12,8
AB	15	3,8	1	2,5
Total	393		39	

Selon le rapport du Prof. *A. Linder* [1] (Laboratoire de statistique mathématique appliquée de la Clinique Ophtalmologique du Prof. *A. Franceschetti*), la prédominance du groupe A dans le syndrome de *Kimmelstiel-Wilson* est signifigative.

Le diagnostic histologique a pu être confirmé par le Prof. *E. Rutishauser*, directeur de l'Institut Anatomo-patologique de Genève.

d) Parmi nos 432 diabétiques, 91 présentèrent une rétinite diabétique assez marquée (Clinique Ophtalmologique de Genève, Prof. *A. Franches-*

[1] Nous remercions le Prof. *A. Linder* de son indispensable collaboration.

chetti), avec une plus faible prodominance de groupe sanguin (A) que chez les malades de *Kimmelstiel-Wilson* (tableau 4).

Tableau 4. Répartition des groupes sanguins dans les rétinites diabétiques

Groupe sanguin	Rétinite diabétique Nombre	Rétinite diabétique %
A	43	47,2
B	11	12,0
O	31	34,0
AB	6	6,5
Total	91	

Il nous est pas encore possible de tirer de conclusion quant à la répartition particulière des groupes sanguins dans le syndrome de *Kimmelstiel-Wilson* et la rétinite diabétique. Nos recherches ultérieures viseront la signification de ces constatations significatives.

Bentall, H. H.: Acta genet. *6*, 566–569, 1956/57

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BLOOD GROUPS AND DISEASE. WITH SPECIAL REFERENCE TO STOMAL ULCER AND PERNICIOUS ANEMIA

By H. H. BENTALL

The work which I am about to describe stems primarily from the Department of Surgery, The Postgraduate Medical School of London, but we are fortunate in having many other collaborators in other parts of Great Britain. Most notable is the debt we owe to Dr. *J. A. Fraser Roberts* of the London School of Hygiene, who has been responsible for the entire statistical work.

It was in 1952 that our interest was first aroused in the possibility of a relationship between cancer of the stomach and the ABO blood groups. This led to an investigation—the results of which we published in a paper in 1953 in which we showed that there is a highly significant increase of group A amongst patients with carcinoma of the stomach compared with its distribution in the general population. The following year we showed that there were even more remarkable differences in the blood group proportions in relation to peptic ulceration. We found that group O is strikingly high and the other three groups correspondingly low in patients suffering from peptic ulcer. We found that there was a rise both in gastric and duodenal ulcer with duodenal ulcer showing an even higher frequency of O than gastric but in our series there was not a statistically significant difference between them. Since that time there have been a number of very substantial compilations of the blood groups in peptic ulceration and it is possible to subdivide these diseases and to re-examine the figures with a view to seeking differences within each subdivision. We have endeavoured to discern a difference between the sites of gastric ulceration but we have been unable to find a significant difference between those classified as prepyloric and the remainder of gastric ulcers. Nor have we been able to find a significant difference between the blood groups of patients who have both gastric and duodenal ulcers, and those with single ulcers. Possibly there is a difference to be discovered but such material as we have classified does not permit of its detection. Another group of patients which was excluded from our first series are the anastomotic or stomal ulcers. *Peebles*

Table 1. Stomal ulcer comparison with duodenal ulcer

Centre	Stomal Ulcer		Duodenal Ulcer		Increased relative Incidence in Group O	χ^2
	O	A+B+AB	O	A+B+AB		
1. London	35	18	506	394	1.54	1.94
2. Newcastle	16	11	281	186	0.96	0.01
3. Glasgow	55	24	947	695	1.68	4.34
	159					6.29

Mean Increase in Incidence 1.46

	D. of F.	χ^2
Difference from unity	1	4.88
Heterogeneity	2	1.41

1–2 *Aird* et al., 3 *Brown* et al.

Brown and his co-workers in Glasgow have just published in the British Medical Journal an important series of cases of this type of ulcer and these are their figures combined with those of our own collection (table 1). We find that there is a significantly higher proportion of group O in cases of stomal ulcer than the already high O in duodenal ulcer. The total numbers are small but should these results prove typical we consider that they are of fundamental importance; it is the first time in this field that a change has been shown to be associated with the severity of a disease. It is probably true to say that a patient with an anastomotic ulcer has the severest form of ulcer diathesis.

As we suggested in our last paper, it was most desirable in furthering this work to examine the blood groups in pernicious anaemia. I will now show you for the first time the results of these investigations, results, it is ironical to note, similar to those obtained by *Buchanan* and *Higley* in 1921, but from which they made a negative deduction (table 2). As you see the

Table 2. Pernicious anaemia

Centre	P.A. O	P.A. A	Control O	Control A	Relative Incidence in Group A	χ^2
London						
Hammersmith	48	75	4,578	4,219	1.70	8.05
Kingston	23	42	4,578	4,219	1.98	6.90
Composite	19	18	4,578	4,219	1.03	0.01
Oxford	112	120	2,888	2,839	1.09	0.41
Cambridge	51	49	1,571	1,501	1.01	0.00
Sheffield	47	58	1,451	1,318	1.36	2.35
Newcastle	55	45	6,598	5,261	1.03	0.02
Glasgow						
Southern General	63	35	3,177	1,906	0.93	0.13
Royal Infirmary	72	61	3,177	1,906	1.41	3.83
Copenhagen [1]	44	47	5,804	6,299	0.98	0.01
						21.71

X = Combined weighted mean incidence in group A. Relative to group O 1.20, 95% Fiducial limits of X, 1.07–1.36

	D. of F.	χ^2	P
Difference from unity	1	8.84	.003
Heterogeneity.	9	12.87	.17

[1] *Køster* et al.

* Full acknowledgment to authors at the centres above are to be found in Brit. med. J. 2, 723, 1956.

frequency of group A is significantly increased in pernicious anaemia. That is to say the difference is in the same direction as in cancer of the stomach.

We have then two diseases of gastric origin with a raised incidence of group A pernicious anaemia and carcinoma of the stomach, and on the other hand we have two diseases, gastric ulcer and duodenal ulcer with a raised incidence of group O; and the highest frequency of group O in that most severe form of peptic ulceration, anastomic ulcer.

It seems very unlikely that these observed differences represent high and low incidence strains in the population. We are therefore forced to the hypothesis that the blood group specific substances themselves, possibly due to their local presence in both gastric mucosa and in gastric secretion are responsible either for being a factor in the production of these two diseases or more probably in protecting against them. It is perhaps possible that all the group specific substances protect against both groups of diseases, but that the A substance is less effective against cancer and the H substance is less effective against ulcer. Some credence was given to this theory when *Clarke* and *McConnell* showed that there is an abnormally high incidence of non-secretors of group specific substance in patients suffering from duodenal ulcer, but one has to bear in mind the concomitance of H substance with A especially in A_2 as described by *Morgan*, a fact which does not however invalidate the theory.

The somewhat tenuous working hypothesis just described would serve to explain the known facts but it is most probable that future discoveries will serve to clarify the matter. It is most clearly necessary to carry this work into the animal laboratory to determine whether these substances can in fact protect against cancer of the stomach or peptic ulceration.

Clarke, C. A. and *P. M. Sheppard:* Acta genet. *6*, 570–574, 1956/57

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THE ABO BLOOD GROUPS IN DUODENAL ULCER
A STUDY OF SIBSHIPS

By C. A. CLARKE and P. M. SHEPPARD

You will by now all be aware that many workers have found an association between blood group O and peptic ulcer. Table 1 shows you our series from Liverpool collected shortly after the publication of the paper by *Aird* and his colleagues in 1954. You will see that in gastric ulcer the percentages are very similar to the controls (blood donors), whereas in duodenal ulcer, group O is greatly increased at the expense of groups A and B.

Table 1. Liverpool data

	O	A	B	AB
Duodenal ulcer, 860	505	263	62	30
Percentages.	58.72	30.58	7.21	3.49
Gastric ulcer, 377	185	151	31	10
Percentages.	49.07	40.05	8.22	2.65
Controls 15,377	49.0	39.1	9.4	2.5

Now the problem with which this communication is concerned is whether the association between group O and duodenal ulcer is or is not causal. By causal, we mean that the O gene is exerting either a direct or pleotropic effect which causes or helps to cause ulcer. By non-causal, we mean that there is no such direct or pleotropic effect. In 1954 we rather took it for granted that the relationship was causal, and as reports of

similar findings came in from other parts of the world, it seemed more and more obvious. It was Professor *Penrose* who first sowed the seeds of doubt. He put it to us rather like this: "If you were to find an association in cosmopolitan Liverpool between group B and dark hair, you would not jump to the conclusion that B caused dark hair. You would say that the finding was probably due to a racial group living with the general population but not mating at random with it." *Penrose* thought it was perfectly possible that there might be a similar type of grouping to account for the ulcer findings, a strain high in O and high in duodenal ulcer but with no causal connection. He said most emphatically that before causality could be accepted, family studies should be done, and this is what we have been doing for the last 18 months. In all the other series that have been published, the controls have been blood donors or overall grouped hospital populations, but in our family studies it is the unaffected sibs who act as controls and these cannot be criticized on the ground that they do not come from the same population as the ulcer patients, and so stratification is avoided. So far we have collected 293 sibships. The propositi were either our own hospital patients or obtained from the local research committee of the College of General Practitioners, to whom we are very grateful. The sibs, of course, were obtained through the propositi. The propositi, the affected and the unaffected sibs were all scored for their ABO blood group and duodenal ulcer status.

The diagnosis in the case of the propositi and affected sibs was always confirmed by X-ray or macroscopic evidence and where there was any doubt about the unaffected sibs we usually managed to get an X-ray performed. So we think that the data from the point of view of diagnosis is reasonably trustworthy.

Table 2. Duodenal ulcer sibships. Blood groups percentages

	O	A	B	AB
Propositi (293)	56.6	29.3	9.9	4.1
Affected sibs (85)	56.5	32.9	9.4	1.2
Unaffected sibs (429).	53.1	31.9	10.7	4.3
Liverpool control	48.9	39.1	9.5	2.5

Table 2 shows you the results of these 293 sibships using all the material. It is not a very accurate method of analysis because it does not take into account family size, but it gives an indication of how things are going.

Let us next consider the matter theoretically. If O were causal you would expect the unaffected sibs in group O to lie near to the general population control figure or at any rate nearer to this figure than to the propositi and the affected sibs. If on the other hand stratification were present the unaffected sibs would be higher in group O than in the general population and would lie closer to the propositi and affected sibs. You will see in table 2 that in group O the unaffected sibs somewhat sit on the fence but they are a little nearer to the propositi and affected sibs than to the controls. In group A the figures for the propositi, affected and unaffected sibs are all very much the same and quite distinctly different from that of the general population.

Now as we said before this method is not very accurate because it does not take into account family size. We have, therefore, analysed our data in a different way using the method which Dr. *C. A. B. Smith* of the Galton Laboratory, London, taught us.

The principle of *Smith*'s method is to assess in each segregating family the chance of the propositus being O and then to compare the total observed results with the total expected. Let us consider the simplest possible case, that of a duodenal ulcer sibship consisting of four persons, two of whom are group O and two of group A. Clearly the chance of the propositus being group O is an even one and this is scored as 0.5. If in fact the propositus is group O the observed score is 1 whereas if he is group A the observed score is 0.

Table 3 shows you the results in the 112 segregating sibships.

Table 3. Analysis of D. U. sibships (method of C. A. B. Smith)

	Propositus group O
Expected	55.243
Observed	59
Difference	+ 3.757
Standard error	5.093
Probability	> 0.4

As you will see, the observed score is slightly higher than the expected but nowhere near significantly so. To be significant the difference between the observed and the expected should be at least twice the S.E. whereas you see the figure does not even reach the level of S.E. So what we feel is that our investigations do not give any significant support to the hypo-

thesis that in duodenal ulcer sibships, a group O person is more likely to have the duodenal ulcer than are his non-O sibs. We do not feel, however, that we have proved a case against causality, although it seems probable that if the association were going to show up within families it would have done so in the nearly 300 sibships. It also seems likely that if O were causal it should show up in sibships where the environment is more likely to be constant and ulcerogenic than where blood donors are used as controls.

We are puzzled about the difference in the results which are obtained when we use, on the one hand, the unaffected sibs and, on the other, the general population as controls. We do not feel very attracted to the idea of stratification since it seems unlikely that the same stratification would occur in such widely separated areas such as England, Denmark, Norway, Portugal and the U.S.A. On going back to our own Liverpool cases we have investigated in a small way the possibility of a Scots or Irish stratification which seemed on the cards. We counted among our ulcer patients those people whose surnames began with Mac or O' and we compared the percentage with that of the general hospital population, but there was practically no difference between the two—so that there is not likely to be a marked Scots or Irish stratification in our ulcer cases. We, therefore, do not know the reason for the discrepancy between the two sets of results, but there is a hypothesis which could explain it, invoking a maternal factor—although you may feel this is rather far fetched. The hypothesis is this: If mothers who are group O are more likely than mothers who are groups A, B or AB to produce children who will develop duodenal ulcer, irrespective of their blood group, the ulcer population would be being bred from a high O strain and would give you the type of result that you saw in table 1, higher in O than in the general population. However, the association would *not* show up in sibships because the effect would be a maternal one and be communicated to the children whatever their ABO blood group. Such a maternal effect might operate immunologically or as a behaviour difference between O and non-O women. Such behaviour differences are well recognized in lower organisms but have never, so far as we know, been described in Man. We think it just worth while to test wherever possible the blood groups of the mothers of ulcer patients to see if there is any support for this hypothesis.

To summarize, therefore, we can say that a study of 293 duodenl ulcer sibships does not give any significant support to the hypothesis that a group O individual is more likely to have the duodenal ulcer than are the sibs of A, B or AB groups.

This paper will be published in full in the British Medical Journal, reference as below.

REFERENCE

Clarke, C. A., J. W. Edwards, D. R. W. Haddock, A. W. Howel Evans, R. B. McConnell and *P. M. Sheppard:* The ABO blood groups and secretor character in duodenal ulcer. Brit. med. J. *2*, 725, 1956.

Discussion

B. Woolf (Edinburgh): I think many members of the audience are a little worried about whether the statistical methods used may not introduce bias.

C. A. B. Smith (London): The method of analysis of the sibships was specially constructed in order to avoid any at present predictable kind of bias though it may not be the most efficient method possible. The assumption underlying the test is that if a family contains, say, two O children and one A, then in the absence of association between ulcer and blood group an ulcer patient in the family is twice as likely to be O as to be A. The same kind of reasoning will apply however many O sibs are present. A detailed discussion will be published elsewhere.

McConnell, R. B. and *P. M. Sheppard:* Acta genet. *6*, 574–579, 1956/57

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THE SECRETOR CHARACTER AND DISEASE

By R. B. McCONNELL and P. M. SHEPPARD

The possible selective effects of the secretion or non-secretion of the ABH antigens has been discussed (*McConnell* [1956]) and part of the duodenal ulcer data presented in this communication has been reported (*Clarke* et al. [1956]). In the latter paper is described the serological techniques used and the mathematical methods employed in the analyses. In this abstract we report the results in an enlarged series of duodenal ulcer patients and data for four other conditions. The anti-H used in testing all these patients was an extract of the seeds of *Ulex europeaus* as this was

found to be much more satisfactory than the eel serum used in the earlier stages of the investigation.

Material

For the past three years we have collected specimens of saliva from patients suffering from various conditions. The first disease to be studied was carcinoma of the stomach but the numbers tested are not yet sufficiently large for any useful conclusion to be drawn from them. In four other conditions, however, a more satisfactory size of sample has been obtained. Duodenal ulcer was an obvious choice for investigation and diabetes mellitus has been studied because of the possible relationship with blood group A (*McConnell* et al. [1956]). Patients with allergic diseases were available in large numbers and the work of *Struthers* [1951] on group A and deaths from broncho-pneumonia in infancy had some bearing on the decision to include asthma in the investigation. Carcinoma of the cervix was chosen because it is a cancer of a mucus secreting tissue which has, with treatment, a good survival time and therefore adequate numbers of patients can be found. The control group consisted of nurses, students and soldiers.

Results

The overall results are shown in table 1. It can be seen that the percentage of non-secretors in all the conditions studied is very similar to that in the controls except in the case of duodenal ulcer and females with carcinoma of the stomach. The number of the latter is too small for any significance to be attached to the difference from the female controls. In duodenal ulcer the number of non-secretors is significantly higher than in the controls ($\chi^2_1 = 13.97$, $P < 0.001$), suggesting that non-secretors may

Table 1. Percentages of non-secretors in controls and patients.

	Males No.	Males % non-sec.	Females No.	Females % non-sec.
controls	335	22.4	156	28.2
duodenal ulcer	525	33.7	106	38.7
diabetes mellitus	190	23.7	128	28.1
allergic diseases	185	23.8	170	27.1
carcinoma of stomach	65	21.5	21	9.5
carcinoma of cervix	—	—	219	28.3

Table 2. Numbers of secretors and non-secretors in 491 controls and 631 duodenal ulcer patients.

Blood group	Secretor status	Controls males	Controls females	Duodenal ulcer males	Duodenal ulcer females
O	secretors	91	43	175	38
	non-secretors	25	17	93	24
A	secretors	123	51	132	14
	non-secretors	38	20	55	13
B	secretors	37	14	29	11
	non-secretors	12	4	21	3
AB	secretors	9	4	12	2
	non-secretors	0	3	8	1

be more liable to develop this condition than are secretors. The addition of a further 117 patients to the series reported by *Clarke* et al. [1956] has not altered the significance of any of the comparisons to an appreciable extent. The details of the controls and of the 631 duodenal ulcer patients are given in table 2. The proportion of non-secretors amongst patients of group O is not significantly different from those of the other ABO groups (table 3).

Table 3. Percentages of non-secretors in 631 cases of duodenal ulcer and 491 controls

		Group O	Groups A, B and AB
Males	Ulcer	34.7	32.7
	Control	21.5	22.8
Females	Ulcer	38.7	38.6
	Control	28.3	28.1

The data for the other conditions are shown in table 4. In none of them is there heterogeneity for blood group or sex. Of the 355 patients with allergic diseases, 250 had asthma and in them the percentage of non-secretors was 21.7 in the 133 males and 25.7 in the 117 females. Of the 219 carcinoma of cervix patients, the diagnosis was histologically proven in 181 cases and in them the percentage of non-secretors was 29.8.

Table 4. Numbers of secretors and non-secretors in diabetes mellitus, carcinoma of the cervix, and allergic diseases.

Blood group	Secretor status	Diabetes mellitus males	Diabetes mellitus females	Carcinoma of cervix	Allergic diseases males	Allergic diseases females
O	secretors	43	39	78	66	64
	non-secretors	12	17	28	19	20
A	secretors	84	44	65	53	46
	non-secretors	27	15	23	21	23
B	secretors	14	6	10	18	10
	non-secretors	4	2	6	3	3
AB	secretors	2	3	4	4	4
	non-secretors	4	2	5	1	0

Sex Difference

A higher proportion of non-secretors was found in the female than in the male controls and the difference was present in those of all four blood groups. On the numbers available this sex difference is not significant ($\chi^2_1 = 1.96$) but similar differences have been found in each of the diseases investigated. If all the male data, excluding duodenal ulcer and carcinoma of the stomach, are combined and compared with the combined female data, the difference between the proportion of secretors in the two sexes is just significant at the 5 % level. This finding of a sex difference is most unexpected and is, at present, inexplicable. It is not considered likely that it could be due to an effect of lipstick for samples of saliva taken before and after the application of lipstick were found to inhibit anti-sera to the same titre.

Secretor Status within Duodenal Ulcer Sibships

Having found a relationship between duodenal ulcer and non-secretion, the question arises whether or not it means that non-secretors are more liable to develop duodenal ulceration than are secretors. For the same reasons as those put forward by *Clarke* and *Sheppard* when considering the relationship between blood group O and duodenal ulcer in an earlier paper to this Congress, it is desirable to carry out family studies to demonstrate whether or not a non-secretor is more liable to develop an ulcer than are his secretor sibs. Such an investigation has been in progress for some time

and table 5 shows data compiled from the 212 sibships in which eel serum was not used in secretor testing. It can be seen that the percentage of non-secretor in the unaffected sibs (112 males, 165 females) is considerably lower than in those with duodenal ulcer and much nearer to the percentage

Table 5. Secretor status in duodenal ulcer sibships excluding those in which eel serum was used.

	Number	% Non-secretors
Propositi	212	36.8
Affected sibs	52	44.2
Unaffected sibs	277	31.4

found in the females of the general population. Table 6 shows the results of analyses using the method described by *Clarke* et al. [1956]. When all the sibships are included there is a significantly higher number of non-secretor propositi than expected. When those sibships in which eel serum was used are excluded there is still a larger number than expected but the difference is not significant. The collection of further sibship data is in progress.

Table 6. Analysis of 95 D. U. sibships segregating for secretor character.

	Propositus non-secretor	
	incl. eel (95)	exl. eel (66)
Observed	55	42
Expected	45.16	35.43
Difference	+ 9.84	+ 6.57
Standard error	4.77	4.20
Probability	< 0.04	> 0.1

Conclusion

The results so far in the duodenal ulcer sibship investigation, suggest that the relationship found between non-secretion and duodenal ulcer in the general population is also present within families. If this is correct it is likely that there is an aetiological relationship between the two and that non-secretor individuals are about 45 % more likely to develop duodenal

ulcer than are secretors. Such an aetiological relationship would suggest that the ABO blood group genes influence the disease by an effect of the antigens which they produce rather than by a pleotropic effect on the type of gastric mucosa or on the acidity of the gastric juice. The discussion of the theory that the antigens, being mucopolysaccharides, may protect the duodenal mucosa and of the possible importance of the secretion of the Lewis substances has been reported (*Clarke* et al. [1956]).

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Discussion

Ph. Levine (Raritan, New Jersey): Dr. *Morgan*, if I may be permitted to restate his remarks, believes that the presumed lack of protection by non-secretors does not imply the absence of mucins. The only chemical difference between secretors and non-secretors is the absence of short chain terminal groupings which determine A, B or H specificity. It is not likely that the absence of these groupings could play any role in the etiology of duodenal ulcer.

Mayr, E., L. K. Diamond, R. P. Levine and *M. Mayr:* Acta genet. *6*, 580, 1956/57

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A SUSPECTED CORRELATION BETWEEN BLOOD GROUP FREQUENCY AND CHROMOPHOBE ADENOMA OF THE PITUITARY

By E. MAYR, L. K. DIAMOND, R. P. LEVINE and M. MAYR

In 123 cases of chromophobe adenoma of the pituitary there was a great deficiency (50.7 per cent) of A and increase of O (31.35 per cent) as compared to 637 brain tumor cases from the same hospitals. The ABO frequency of these brain tumors agrees reasonably well with a large sample of the Massachusetts population (N=120,281).

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LEGAL APPLICATION OF BLOOD GROUPS AND OTHER ANTHROPOLOGICAL TRAITS

Saller, K.: Acta genet. *6*, 581–590, 1956/57

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ANTHROPOLOGIE UND VATERSCHAFTS-NACHWEIS

Von K. SALLER

Der anthropologische Vaterschaftsnachweis ist eine der praktischen Konsequenzen, zu denen die Erbforschung für den Menschen geführt hat. Er befaßt sich damit, in zweifelhaften Fällen mit mehr oder minder großer Sicherheit den Vater eines Kindes festzustellen «Mater certa, pater semper incertus» war schon eine altrömische Aussage. Solche zweifelhafte Fälle sind vor allem sehr viele uneheliche Kinder, für welche Mehrverkehr der Mutter feststeht oder auch Ehelichkeitsanfechtungen. Aber auch Findel- oder Flüchtlingskinder, die in den Wirren der Zeit ihren Eltern abhanden gekommen sind, können Gegenstand eines sogenannten «Vaterschaftsnachweises» werden; in solchen Fällen waren mehrfach nicht nur strittige Vater-Kind-Beziehungen zu beurteilen, sondern ebenso Mutter-Kind-Verbindungen, zum Teil sogar von erheblicher politischer Bedeutung.

Der Aufgabenstellung für den Vaterschaftsnachweis entspricht es, daß über ihn die meisten Erfahrungen dort bestehen, wo viele uneheliche Kinder nicht nur gezeugt, sondern auch ausgetragen werden, und wo die gesetzlichen Bestimmungen festlegen, daß nicht etwa alle am Mehrverkehr beteiligten Männer für das Kind zu zahlen haben, sondern daß ein ganz bestimmter Mann als Vater des Kindes haftbar gemacht werden muß. Betrachtet man die Gesamtsituation für Anthropologie und Vaterschaftsnachweis durch einen Überblick über die verschiedenen Länder, dann ist zu sagen, daß derartige Bedingungen in Deutschland offenbar strenger und sehr viel häufiger gegeben sind als in anderen Ländern und innerhalb Deutschlands wieder in Bayern häufiger als in den anderen Bereichen der Bundesrepublik. Es ist unmöglich, in der zur Verfügung stehenden Zeit den

ganzen Schatz von Erfahrungen auszubreiten, die wir in einer solchen Situation bisher mit Vaterschaftsgutachten, ihren Ergebnissen und ihrer Problematik, haben sammeln können. Auch soll von vornherein nur eine Einführung in das ganze Thema gegeben werden. Daher will ich mich mit der nachfolgenden Darstellung auf einige der wichtigsten Punkte und vor allem darauf beschränken, das Wesentliche dessen hervorzuheben, was feststeht oder was noch weiter erforscht werden muß oder kann. Zu Einzelheiten, die über meinen allgemeinen Rahmenvortrag hinausgehen, werden die folgenden Vorträge noch Ergänzungen und Erweiterungen bringen.

Die Beziehungen eines Kindes zu seinen fraglichen Vätern oder auch zu einer fraglichen Mutter haben zwei Seiten, nämlich eine negative und eine positive Seite, und sie sind auch sonst mit einer mannigfachen Problematik belastet.

Die *negative* Fragestellung, d. h. ein Ausschluß im Abstammungsverfahren kann einfacher liegen als der positive Vaterschaftsnachweis. Sie geht dahin, ob und welche von mehreren in Betracht kommenden Vätern für das strittige Kind ausgeschlossen werden können. Wir bezeichnen Merkmale, die einen solchen Ausschluß gestatten, als «Ausschlußmerkmale». Ihre Anwendung genügt dort, wo die Zahl der in Betracht kommenden «Väter» feststeht und dann die Untersuchung mit Hilfe eben dieser Ausschlußmerkmale alle Väter bis auf einen von der Vaterschaft ausschließt. Dieser eine ist dementsprechend der Vater. Der *positive* Vaterschaftsnachweis befaßt sich dort, wo mit den Ausschlußmerkmalen nicht zum Ziel zu kommen ist, mit den Ähnlichkeiten des umstrittenen Kindes und den in Betracht kommenden Vätern unter Berücksichtigung und kritischer Wertung aller Ähnlichkeiten des Kindes auch mit seiner Mutter und eventuell auch der Mutter mit den in Betracht kommenden Vätern. Je nach den Ähnlichkeiten des Kindes mit den verschiedenen in Betracht kommenden Vätern bzw. einem von ihnen wird dann von verschiedenen Wahrscheinlichkeitsgraden der Vaterschaft gesprochen und damit eine bestimmte Vater-Kind-Beziehung festgelegt, welche den Gerichten die Unterlage für ein abschließendes und endgültiges Urteil abgeben kann.

Zumal für den positiven Vaterschaftsnachweis ergeben sich verschiedene zusätzliche Probleme.

Ein erstes Problem, das wir auch als Anthropologen zu beachten und zu berücksichtigen haben, folgt aus der praktischen Zusammenarbeit zwischen Juristen und Anthropologen. Es besteht darin, daß der Biologe gelegentlich aus seinen Untersuchungen bisher nur auf eine 60- oder 80-, selbst 90- bis 99%ige Sicherheit schließen kann. Der Jurist aber kann mit solchen Prozentzahlen nichts anfangen und hat darüber zu entscheiden, ob ein Mann

mit 100 %iger Sicherheit, d. h. ob er eben einfach der Vater ist oder ob er es nicht ist. 80 %ige oder 20 %ige Väter oder Nichtväter kann es ja in Wirklichkeit nicht geben. Es muß Aufgabe einer Verfeinerung unserer Beobachtungs- und Bearbeitungsmethoden sein, in möglichst allen Fällen zum höchsten Wahrscheinlichkeitsgrad zu gelangen, den eine biologische Forschung überhaupt geben kann, nämlich zu einer «an Sicherheit grenzenden Wahrscheinlichkeit» mit einem «für das praktische Leben hinreichenden Genauigkeitsgrad». Statistisch bedeutet das nach der bisherigen Konvention etwa eine 99,7 %ige Sicherheit (d. i. 3 σ); doch befindet sich gerade diese Konvention sowohl bei den Biologen als auch bei den Juristen noch in der Diskussion.

Ein weiteres, mehr biologisches Problem, das im positiven Vaterschaftsnachweis berücksichtigt werden muß, ist das der Graduierung der Merkmale und ihrer unterschiedlichen Geschlechts- und Altersmanifestierung. Wir kennen Alternativmerkmale mit nur der einen oder einer anderen Ausprägung; hier liegen die Verhältnisse einfach. Wir kennen aber auch – und dabei handelt es sich um die Mehrzahl gerade der anthropologischen Merkmale für den Vaterschaftsnachweis – Merkmale mit einer breiten und auch geschlechtsverschiedenen Schwankung ihrer Ausprägung und zugleich Verschiebung dieser Ausprägung mit dem Alter. Hier besteht das Problem darin, daß dieselbe rechnerische Einheit, etwa 1,0, weder im Vergleich der verschiedenen Merkmale noch der verschiedenen Altersstufen oder Geschlechter miteinander denselben Wert hat und dasselbe bedeutet. Hier müssen also mit einer Normierung verschiedene zusätzliche Vorkehrungen getroffen und Gesichtspunkte berücksichtigt werden, durch die einwandfreie und brauchbare Vergleiche sichergestellt werden.

Ein letztes Problem schließlich, das hier ebenfalls noch kurz gestreift werden soll, ist das der Objektivierung aller Befunde und Abstrahierung des Ergebnisses von der Autorität des betreffenden Beobachters. Es kann in einer naturwissenschaftlichen Disziplin wie der Anthropologie und damit auch für den Vaterschaftsnachweis auf die Dauer nicht angehen, die Probleme auf Grund geringerer oder größerer Erfahrungen durch den einzelnen Beobachter autoritär zu entscheiden. Vielmehr müssen auch hier Methoden gefunden werden, die eine auch von anderen Untersuchern jederzeit nachprüfbare Urteilsbildung ermöglichen, sobald nur die unvorgenommen erhobenen Untersuchungsbefunde erst vorliegen. Es handelt sich hier um besondere statistische Methoden, und wir sind dabei, auch solche statistische Methoden zu immer größerer Zuverlässigkeit zu entwickeln.

Für Einzelheiten in der Problematik des Vaterschaftsnachweises, die damit in kurzem Überblick gezeigt ist, sei zunächst zu den sogenannten

Ausschlußmerkmalen Stellung genommen. Angesichts der einfachen Eleganz, mit der durch solche Ausschlußmerkmale über eine Vaterschaft entschieden werden kann, liegt auf der Hand, daß nach ihnen immer wieder und in erster Linie gesucht wurde und gesucht wird. Die Einfachheit eines solchen Ausschlusses war bei einzelnen Merkmalen geradezu eine Versuchung, sie für Ausschlußmerkmale zu erklären, obwohl sie bei kritischer Betrachtung keine solchen waren. Damit ist bei früheren Vaterschaftsnachweisen manches Unheil angerichtet worden. Als anerkannte Ausschlußmerkmale für den Vaterschaftsnachweis sind heute verschiedene Bluteigentümlichkeiten anzuführen, außerdem aber dann auch einige morphologisch-anthropologische Merkmale, die für die Vaterschaftsentscheidung gewisse Anhaltspunkte geben sollen.

Unter den Bluteigentümlichkeiten gelten als Ausschlußmerkmale die sogenannten klassischen Blutgruppen, d. h. das ABO-System mit Unterabteilungen, dann die MN-Faktoren, das Rhesus-System und einige andere Faktoren. Auch die Untergruppen im Rhesus-System sind heute so weit erforscht, daß sie, von gewissen technischen Schwierigkeiten abgesehen, wenigstens grundsätzlich als Ausschlußmerkmale angesprochen werden können, wenngleich Einzelheiten dafür noch vielfach der Diskussion bedürfen und auf ihre Problematik auch in den Gutachten praktisch hingewiesen werden muß. Jedenfalls gelingt es mit Hilfe der Bluteigentümlichkeiten heute für rund 50 % der Vaterschaftsuntersuchungen zu einer Entscheidung zu kommen, die weitere Untersuchungen im Sinn des positiven Vaterschaftsnachweises unnötig macht. Als unbrauchbar hinsichtlich seiner ausschließenden oder auch nur positiven Bedeutung für den Vaterschaftsnachweis hat sich der sogenannte *Löns*-Test erwiesen. Er ist nicht nur in seiner theoretischen Fundierung zweifelhaft, sondern auch in der Praxis durch verschiedene Untersucher nicht zu gleichen Ergebnissen reproduzierbar. Seine Befunde können dementsprechend für den Vaterschaftsnachweis heute nicht anerkannt werden. Für alle Blutmerkmale, die als Ausschlußmerkmale brauchbar sind, hat sich im übrigen ein einfacher Erbgang ihrer Alternativausprägungen ergeben, so daß durch die Einfachheit ihrer Feststellung auch eine klare Entscheidung möglich wird.

Für die morphologisch-anthropologischen Merkmale, die als Ausschlußmerkmale in Betracht kommen, liegen die Verhältnisse komplizierter. Hier handelt es sich nicht um monomere, eventuell allele Faktoren, sondern um polymere Merkmale und vielfach auch plastische Entwicklungsgänge vom Gen zum Phän, welche die in Betracht kommenden Merkmale bedingen. Daher kann tatsächlich nur in der Kombination extremer Ausprägungsgrade gelegentlich für diese Merkmale eine ausschließende Vaterschafts-

entscheidung herbeigeführt werden. Immerhin sind jedoch auch mit Hilfe dieser Merkmale gelegentlich Vaterausschlüsse möglich.

So liegen die Dinge etwa für die Komplexion, d. h. Augen-, Haar- und auch die Hautfarbe. Für sie ist – in Polymerie – eine starke Pigmentierung dominant über das Fehlen der Pigmentierung oder eine sehr schwache Pigmentierung. Man wird also aus der Kombination zweier pigmentloser oder äußerst pigmentarmer Individuen keinesfalls dunkelpigmentierte Kinder erwarten können, während umgekehrt hellpigmentierte Kinder aus der Verbindung beidseitig dunkler Eltern in einer mischerbigen Bevölkerung durchaus möglich sind. Ähnlich verhält sich die Haarform, bei der extrem gekrümmte Formen (Spiraldrehung) ebenfalls dominant sind über die gerade Form, so daß aus der Verbindung solcher geraden Formen keine extrem spiralhaarigen Kinder zu erwarten sein werden. Einen Sonderfall für die Verhältnisse bei den Haaren stellt die Rothaarigkeit dar. Sie scheint sich grundsätzlich, wenn auch mit gewissen Komplikationen, einfach recessiv gegen braune Haarfärbung zu vererben und damit unter die Alternativmerkmale zu fallen. Andere anthropologische Merkmale sind in ihrer Bedeutung als Ausschlußmerkmale von vornherein unkritischer, d. h. viel zu umfassend eingesetzt und gedeutet worden. Das gilt vor allem für den röntgenologischen Wirbelsäulenvergleich. Für die Befunde an der Wirbelsäule ist zunächst eine einfache Dominanz der kranialen Variationstendenz über die caudale auf Grund eines einzigen allelen Paares angenommen worden. Tatsächlich erwies sich jedoch auch diese Variabilität als polymer bedingt und dementsprechend wie für die anderen angeführten anthropologischen Merkmale eine Ausschlußmöglichkeit nur bei Kreuzungen von Extremvarianten als gegeben. Vollends unbrauchbar war der Versuch, nach einem metrischen Merkmal wie der Ohrbreite einen Vaterschaftsausschluß zu tätigen auf Grund der Annahme, daß die große Ohrbreite einfach dominant sei gegen die kleine. Das mußte jedem von vornherein einigermaßen klar sein, der über das Wesen anthropologischer Maße nachgedacht hat. Es hat sich dann auch in der Praxis entsprechend erwiesen; die Auswertung von Ohrbreitenunterschieden als Ausschlußmerkmal ist heute allgemein fallengelassen.

Schließlich sei zu den Ausschlußmerkmalen auch noch auf die seltenen monofaktoriell bedingten Erbabartungen oder Erbkrankheiten verwiesen, welche die etwa mit der Rothaarigkeit angeschnittene Kategorie von Merkmalen fortführen, so die Brachydaktylie oder die Bluterkrankheit oder dergleichen. Soweit es sich dabei tatsächlich um seltene Merkmale in der betreffenden Bevölkerung handelt, können solche Merkmale zuletzt nicht nur als Ausschlußmerkmale fungieren, sondern mit einem unter Umständen

erheblichen Gewicht auch für den positiven Vaterschaftsnachweis beigezogen werden.

Zum *positiven Vaterschaftsnachweis* ist zu sagen, daß er ganz allgemein die Feststellung größerer oder geringerer Ähnlichkeit zwischen dem Kind und den als Vater in Betracht kommenden Männern anstrebt. Solche Ähnlichkeiten müssen schließlich als Ganzheit gewertet, d. h. es darf im Rahmen des Gesamtvergleichs kein Einzelmerkmal über- oder unterbewertet werden. Aber die Ähnlichkeitsbeurteilung baut sich doch aus der Beurteilung von Einzelmerkmalen auf, die entsprechend bestimmt und dann ausgewertet werden müssen. Hier liegen die Probleme. Wir sind einstweilen bestrebt, zum positiven Vaterschaftsnachweis möglichst viele Einzelmerkmale beizuziehen. In unseren jetzigen Untersuchungsbögen sind es zwischen 150 und 200, einschließlich somatometrischer, somatoskopischer, daktyloskopischer usw. Befunde, und es ist selbstverständlich unmöglich, für die grundsätzliche Diskussion auch zwecklos, sie hier alle zu nennen. Genetisch liegt das Problem für die Vielzahl dieser Einzelmerkmale darin, daß sie nicht monofaktoriell, sondern polymer bestimmt, also nicht genetisch einfach sinnvoll, sondern vielfach nur durch unsere Beobachtungs- und Meßtechnik abgegrenzt sind. Wie weit genetisch einfach und womöglich monofaktoriell bestimmte Eigentümlichkeiten auch zu einem positiven Vaterschaftsnachweis beigezogen werden können, ist bereits oben kurz erläutert: derartige Merkmale haben ein um so größeres Gewicht, je seltener sie in der Gesamtbevölkerung vorkommen, welcher die Probanden entstammen. Für die sicher polymer bestimmten und in der Ganzheit einer Konstitution durch mannigfache Korrelationen geprägten anthropologischen Merkmale kommen wir mit einer weiteren Genanalyse, so wie die Dinge heute sich ansehen, offensichtlich nicht weiter. Trotzdem haben wir aber auch hier die Möglichkeit und für die weitere Verbesserung unserer Gutachten und ihrer Ergebnisse ist es eine Notwendigkeit, aus dem jetzt sehr umfassenden und etwas diffusen Ähnlichkeitsvergleich zu präziseren Auffassungen und zu einer zuverlässigeren Wertung von Einzelmerkmalen in der Gesamtzahl der berücksichtigten Eigentümlichkeiten zu kommen.

Von der biologischen Seite her sind dazu vor allem zwei Möglichkeiten gegeben, deren erste wir bereits eingehend bearbeitet und deren zweite wir inzwischen auch wenigstens in Angriff genommen haben.

Die erste Möglichkeit ist eine Prüfung des Beweiswertes verschiedener Merkmalskomplexe in Mutter-Kind-Verbindungen, d. h. eine einschränkende Weiterführung der Untersuchungen ganzer Familien, die selbstverständlich wie bisher zu den Problemen der Vaterschaftsgutachten beitragen können; ihrer Bearbeitung hat sich an meinem Institut vor allem *Baitsch*

zugewendet. Die Mutter-Kind-Verbindungen sind in den Vaterschaftsuntersuchungen, die wir durchzuführen haben, gesichert, während die Vater-Kind-Verbindungen ja unsicher sind und erst festgestellt werden müssen. Wenn wir also aus unseren Erhebungen das Mutter-Kind-Material herausnehmen und getrennt daraufhin untersuchen, für welche Merkmalskomplexe in diesen Verbindungen die Mutter-Kind-Beziehungen gewichtiger sind als für andere, dann bekommen wir damit einen Anhaltspunkt auch für die unterschiedliche Bedeutung der einzelnen Merkmalskomplexe im Abstammungsnachweis überhaupt, also auch für den Vaterschaftsnachweis, auf den es in den allermeisten Fällen unserer Untersuchungen ja ankommt. Allerdings muß für eine derartige Ausweitung unserer Untersuchungsergebnisse an Mutter-Kind-Verbindungen ausgeschlossen werden, daß nicht auch beim Menschen eine plasmatische und auf die Mutter beschränkte Übertragung vorkommt. Unsere bisherigen Untersuchungen zeigen, daß eine derartige matrokline Übertragung, wenn sie überhaupt stattfindet, für die in Betracht kommenden Jahrgänge bei den von uns berücksichtigten Merkmalen kaum ins Gewicht fällt. Unter solchen Voraussetzungen haben sich in unseren Untersuchungen überraschenderweise Ohrmerkmale (Ohrlage am Kopf, Ohrgröße, Gesamtrelief, Scheitelhöhe, Helixeinrollung, Helixbreite, Anthelixbiegung, Breite der Incisura intertragica) als von verhältnismäßig großem Beweiswert erwiesen; wir sind nicht unbedingt sicher, ob dieser Befund ganz objektiv ist und nicht schon bei der Erhebung der Ohrmerkmale durch den Beobachter in gewissem Grad, wenngleich unbewußt, durch eine vorgefaßte Meinung mitgeprägt wird und prüfen diesen Verdacht augenblicklich nach. Weiter erwiesen sich gewisse Plantamuster (vor allem der Interdigitalfelder 1 rechts und links, Interdigitalfeld 2 rechts und links, Interdigitalfeld 3 rechts und links, Triradius rechts und links) als von hohem Beweiswert. Es folgen Augenfarbe und Irisstruktur, deren Beweiswert etwa dem der restlichen Plantamuster, von Fingerbeerenmustern, von Mustern der Palma und der metrischen Merkmale entspricht. Von *relativ* geringem wenngleich *absolut* immer noch beträchtlichem Beweiswert erwiesen sich gewisse Fingerbeerenmuster (Kompliziertheitsindex, Eltern-Kind-Differenzwert im Kompliziertheitsindex, Leistenhöchstwert der Polsterwertsumme, Auftreten von Wirbeln, Auftreten von Muschelschleifen) sowie gewisse andere Muster der Palma (Endfeld A-Linie recht und links, Hypothenarmuster rechts und links, Thenarmuster rechts und links, weiter Interdigitalfeld 2 rechts und links, Interdigitalfeld 3 rechts und links, Interdigitalfeld 4 rechts und links, Anzahl der axialen Triradien rechts und links). Dieses Ergebnis bedeutet nicht, daß die weniger gewichtigen Merkmale weniger erbbegründet sind als die

anderen. Die Ursache für die Bedeutungsunterschiede liegen vielmehr einmal in der mit größeren Fehlermöglichkeiten behafteten Beobachtungs- und Abgrenzungstechnik bei manchen weniger bedeutsamen Merkmalen und weiter auch in der größeren Umweltplastizität beim individuellen Entwicklungsgang dieser Merkmale.

Damit ist der Hinweis auf die zweite biologische Möglichkeit zur besseren Präzisierung unserer Vaterschaftsuntersuchungen gegeben, nämlich der Hinweis auf Zwillingsuntersuchungen. Vergleiche zwischen den Partnern eineiiger Zwillingspaare sind ja bekanntlich die Methode der Wahl für Feststellungen darüber, ob ein Merkmal bei seiner Entwicklung vom Gen zum Phän stärker umweltlabil oder umweltplastisch ist. Wir haben für unsere Vaterschaftsuntersuchungen in erster Linie Interesse an umweltstabilen Merkmalen, weniger an umweltplastischen, um damit Einflüsse der Umwelt, die ja immer verschieden ist, für die Endbeurteilung möglichst außer acht lassen zu können. Es wird also darauf ankommen, weiterhin alle Merkmale für den positiven Vaterschaftsnachweis ebenso wie in den Mutter-Kind-Verbindungen auch in Zwillingsuntersuchungen auf ihr Gewicht zu prüfen. Was bisher an Zwillingsuntersuchungen über derartige Unterschiede durchgeführt wurde, kann gerade für die minutiösen Merkmale, die oft in unserem Vaterschaftsnachweis eine Rolle spielen, einstweilen nicht genügen. An meinem Institut sind nun darüber hinausgehende Untersuchungen im Gange, die sich mit dem Zwillingsbefund auch für die im Vaterschaftsnachweis berücksichtigten feineren Merkmale befassen. Über das Ergebnis ist vielleicht einmal später zu berichten.

Noch eine dritte Möglichkeit zur Präzisierung unserer Vaterschaftsgutachten besteht und muß konsequent weiterverfolgt werden. Sie ist nicht unmittelbar biologisch, aber mit den biologischen Möglichkeiten so eng verbunden, daß die eine ohne die andere Methode nicht zum Ziel kommen kann. Es handelt sich um die *rechnerisch-statistischen Verfahren*. Damit wird zugleich das aufgenommen, was bei der allgemeinen Problemstellung über die Notwendigkeit gesagt wurde, unsere Urteile von der Autorität und Erfahrung des einzelnen Beobachters möglichst zu abstrahieren und statt dessen in Unabhängigkeit rein auf die Sache zu objektivieren.

Hier sind die Verfahren zu erwähnen, die alters- und geschlechtsvariablen Merkmale für Kinder und Eltern auf Einheitswerte umzurechnen und damit vergleichbar zu machen. Ein solches Verfahren setzt die Kenntnis der Altersveränderungen und Geschlechtsunterschiede voraus, wie sie in der betreffenden Gesamtbevölkerung sich vollziehen. Wenn eine solche Voraussetzung bei vielen Untersuchungsstellen und für viele Merkmale auch noch nicht restlos erfüllt ist und sich für manche Vergleiche auch überhaupt

nicht erfüllen läßt, so daß diese Vergleiche bis zu einem gewissen Grad ungenau bleiben müssen, so ist doch die Notwendigkeit einer solchen Umrechnung grundsätzlich allgemein anerkannt. Dasselbe gilt für die Feststellung von Genhäufigkeiten für die erblich einfach bedingten Merkmale, wie sie einstweilen vornehmlich nur zu Vaterschaftsausschlüssen gebraucht werden.

Noch in Diskussion sind dagegen die Verfahren, welche schließlich die gemachten Beobachtungen auswerten und unabhängig beurteilen sollen. Hier sind verschiedene Versuche gemacht worden, die bisher nicht exakt zum Ziel geführt haben. Ein Fernziel dieser Forschungsrichtung wird sein, schließlich in der Praxis mit nur noch einem oder doch möglichst wenigen Merkmalen auszukommen, durch die verschiedene Merkmalskomplexe hinreichend gekennzeichnet werden können und nach diesen Merkmalen dann eindeutig zu entscheiden. So weit sind wir einstweilen noch nicht. Doch haben die bisherigen Erörterungen zu diesem Punkt immerhin wenigstens Klarheit darüber gebracht, welche Voraussetzungen für eine statistisch-exakte Verarbeitung der gewonnenen Daten erfüllt sein müssen, um zuverlässig zum Ziel zu kommen. Solche Voraussetzungen sind erstens, wie sich bereits aus den gemachten Ausführungen ergibt, eine möglichst exakte Erfaßbarkeit, zugleich möglichst wenig willkürliche Einteilungsmöglichkeit und auch genaue Kenntnis der Umweltstabilität, Manifestationswahrscheinlichkeit und Häufigkeit des betreffenden Merkmals in der Bevölkerung, der die Probanden entstammen: Je genauer erfaßbar, je sachlicher einteilbar und zugleich je umweltstabiler und seltener eine Merkmalsausprägung ist, desto mehr Beweiswert wird sie haben; zweitens eine Berücksichtigung aller Merkmale möglichst nach Komplexen, zu denen sie biologisch-genetisch zusammengehören (d. h. Merkmalsgruppen mit stärkeren Binnenkorrelationen) und für den Vergleich solcher Komplexe eine Normung der unterschiedlichen Gewichtigkeiten ihrer Ausprägungen: Damit soll die Überbewertung übergeordneter Faktoren, die in den Einzelmerkmalen sonst oft mehrfach zum Einsatz gebracht würden, und die unterschiedliche Bedeutung zahlenmäßig unter Umständen gleicher Abstufungen bei verschiedenen Merkmalen ausgeschaltet werden; und drittens eine Beachtung des Durchmischungsgrades der Gesamtpopulation: In einer völlig durchmischten, unter Umständen eng ingezüchteten Bevölkerung hat das Auftreten eines bestimmten Merkmals bei den Probanden eine andere Bedeutung als in weniger ingezüchteten Populationen von größerem Auskreuzungsumfang; auch die Seltenheit oder größerer Häufigkeit eines Merkmals muß in diesem Zusammenhang unterschiedlich ins Gewicht fallen.

Wir sind dabei, auf der Grundlage solcher Voraussetzungen, die für

unser Münchener Material zum Teil schon erarbeitet sind, ein Verfahren auszuarbeiten, das zugleich dem praktischen Bedürfnis entspricht, möglichst einfach, mit möglichst geringem Arbeitsaufwand und doch wissenschaftlich zuverlässig nicht zu Wahrscheinlichkeitsprozentsätzen, sondern möglichst zu einer Alternativentscheidung mit klar definierten Irrtumswahrscheinlichkeiten zu kommen. Damit soll auch dem Bedürfnis entsprochen werden, auf das uns die Juristen mit ihren Ansprüchen immer wieder hinweisen, nämlich daß in Wirklichkeit nur ein Mann der Vater sein oder nicht sein kann, nie aber mit unterschiedlichen Wahrscheinlichkeitsprozentsätzen verschiedene Väter. Wir glauben auf der Grundlage und in Weiterentwicklung diskriminanzanalytischer Methoden auf einem Weg zu sein, der zum Ziel führt, jedenfalls diesem Ziel mit dem weiteren Ausbau der Methode näher kommen wird als die bisher dazu versuchten Methoden. Doch kann auch über diese im Gang befindlichen Arbeiten erst bei späterer Gelegenheit endgültig berichtet werden; vorläufige Mitteilungen sind dazu bisher von *Baitsch*, weiterhin von *Bauer* gemacht worden.

Damit ist in gedrängter Kürze, wie die verfügbare Zeit sie erfordert, ein Aufriß zum Thema Anthropologie und Vaterschaftsnachweis gegeben. Er sollte zeigen, was wir können und was wir noch nicht können, und zu dem, was wir noch nicht können, wie wir versuchen, weiterzukommen. Die menschliche Erblichkeitslehre hat in der Erforschung sowohl von Erbtransportfragen als auch der Phänogenetik Gewaltiges geleistet. Die Anwendung der Forschungsergebnisse auf die praktischen Fragen des Vaterschaftsnachweises erfordert eine Synthese aller Ergebnisse der verschiedenen Untersuchungsrichtungen und vermag, wie gezeigt werden konnte, in dieser Synthese Entscheidendes zu geben. Wir können mit den heute schon erarbeiteten Methoden der Ausschlußmerkmale und des positiven Vaterschaftsnachweises mehr als 90 % der uns zur Begutachtung übergebenen Fälle zu einer klaren und auch verläßlichen Entscheidung bringen. Zugleich konnte und mußte freilich auch ausgeführt werden, daß gerade die praktischen Forderungen des Vaterschaftsnachweises der wissenschaftlichen Forschung noch viele Aufgaben stellen. Die Fruchtbarkeit jeder Wissenschaft folgt überall aus einem Wechsel- und Zusammenspiel von Forschung und Praxis. So wird sich auch in der Anthropologie durch ihre Beschäftigung mit den Vaterschaftsnachweisen ein Fortschritt für die menschliche Genetik ergeben. Der Zweck meiner Ausführungen war es, dazu einige Wege zu zeigen.

Harrasser, A.: Acta genet. 6, 591–596, 1956/57

FORENSISCHE PROBLEME DER ANTHROPOLOGISCH-GENETISCHEN FESTSTELLUNG DER VATERSCHAFT

Von A. HARRASSER, München

Die Anwendung naturwissenschaftlicher Erkenntnisse zur Beweisführung vor Gericht erfordert:

1. daß die Beweiskraft, also der Grad der Sicherheit der vom Sachverständigen getroffenen Feststellungen und daraus gezogenen Folgerungen in einer dem juristischen Denken entsprechenden logisch-kausalen Darlegung überzeugend ist, und
2. daß die Aussage des Endergebnisses auf die juristischen Umstände zutreffen kann, zu deren Beweis oder Widerlegung das Gutachten eingeholt wird.

Die in dieser Hinsicht zentralen Probleme des anthropologisch-erbbiologischen Gutachtens sollen nun im wesentlichen kurz erörtert werden, wobei Grundlagen und Methoden des Verfahrens hier als bekannt vorausgesetzt werden müssen [1].

Juristisch gesehen ist diese Art der Expertise in ihrer allgemeinsten Definition jede gutachtliche Äußerung, in der auf Grund des Vergleiches von Befunden körperlicher Eigenschaften des Forschungsbereiches der physischen Anthropologie nach den Erkenntnissen der Humangenetik eine Folgerung auf das Abstammungsverhältnis zwischen bestimmten Personen gezogen wird. Für diesen Begriff des Gutachtens ist belanglos, wenn in der Praxis die serologisch erfaßten Gene im sogenannten Blutgruppengutachten in der Regel gesondert behandelt werden; es geschieht dies ja schon aus Zweckmäßigkeitsgründen, weil bei einem schon singulär beweiskräftigen

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[1] Zur näheren Literatur sei verwiesen auf: *Kramp*, Bibliographie zur anthropologisch-erbbiologischen Abstammungsprüfung, *Homo*, Band 2, Heft 2, 1951; *Schade*, Vaterschaftsbegutachtung, Stuttgart 1954.

Vaterschaftsausschluß in einem bestimmten Bluttypensystem sich weitere Untersuchungen erübrigen. Zu betonen ist aber, daß eine erbbiologische Begutachtung im maximalen Umfang sich auf alles beim Menschen Vererbliche und daher auch auf alle erbpathologischen Erscheinungen erstrekken kann. Dennoch erscheint der in Deutschland gebräuchliche Name «anthropologisch-erbbiologisches Gutachten» kennzeichnend, da in den allermeisten Fällen das Schwergewicht ja auf Körpermerkmalen des normalen Variationsbereiches liegt. Das Wesen des Gutachtens erfordert nun, zur Sicherung des Ergebnisses die Basis für Folgerungen in der Beweisführung möglichst zu verbreitern, weil einerseits das Substrat der verwertbaren Merkmale durch eine noch ungenügende Differenzierung mancher Körpereigenschaften des Kindes mehr oder minder stark eingeschränkt sein kann und weil andererseits bei den meisten als vorwiegend anlagebedingt bekannten Teilen des Phänotypus, welche als sogenannte «Merkmale» imponieren, ja Polygenie (unter Umständen auch Polyphänie) angenommen werden muß. Daher ist verständlich, daß bei den nach der Konstellation von Kind, Mutter und dem betreffenden Mann aus solchen Teilbefunden in der Vaterschaftsfrage gezogenen Folgerungen ein Sicherheitsgrad sich nicht nach den auf genotypischer Grundlage, d. h. bei Genhypothesen anwendbaren mathematischen Methoden zahlenmäßig berechnen läßt.

Allerdings liegen auch hinsichtlich solcher Merkmale wohl schon Versuche und Vorschläge zu rechnerischen Methoden für die Vaterschaftsexpertise vor *(Geyer* und *Essen-Møller*, *Keiter*, *Wichmann*, *Baitsch* und *Bauer)*, deren besondere Probleme und Fragen ebenso wie die in theoretischer und praktischer Hinsicht dagegen erhobenen Einwände nicht in diesem Rahmen erörtert werden können.

Für die erste der zu Beginn angegebenen Bedingungen hat nun eine Entscheidung des Deutschen Bundesgerichtshofes den Grundsatz aufgestellt, daß «die dem Gutachten zugrundegelegte Lehre in den maßgebenden Fachkreisen allgemein und zweifelsfrei als richtig und zuverlässig anerkannt» sein soll [2]. Dies steht hinsichtlich der allgemeinen Prinzipien der Humangenetik sicher außer Diskussion, während in Einzelfragen (spezielle Erbgänge usw.) natürlich nie ein Consensus omnium, sondern praktisch nur die im Fachkreis herrschende Auffassung in Betracht kommt. In der Entwicklung des a. e. Gutachtens im Laufe von 25 Jahren haben sich in Deutschland und im wesentlichen analog auch in Österreich nun bestimmte Grund-

[2] Urteil vom 16. 6. 1953. Veröffentlicht in der Neuen Juristischen Wochenschrift, 1954, S. 83.

sätze für die Beurteilung der Sicherheit des Ergebnisses herausgebildet, deren Umgrenzung im folgenden behandelt wird.

Im Sinne des forensischen Beweisthemas mußten wir ausgehen vom Begriff einer in den betreffenden Deutschen Rechtsnormen (§§ 1717, 1951 BGB) durch die Worte «offenbar unmöglich» gekennzeichneten Gewißheit, die Vaterschaft eines bestimmten Mannes zu einem bestimmten Kind auszuschließen. Von der Interpretation dieses Begriffes hängt es also ab, welche Anforderungen von juristischer Seite an die Sicherheit einer Aussage des Gutachtens gestellt werden, weil nur dann beurteilt werden kann, ob und unter welchen Umständen das Verfahren des a. e. Gutachtens einen solchen Grad der Sicherheit zu begründen vermag.

In einer anderen Entscheidung des Deutschen Bundesgerichtshofes wird nun für den Beweis der offenbaren Unmöglichkeit der Vaterschaft «nicht das Vorliegen eines Sachverhalts gefordert, der die Vaterschaft mit denkgesetzlicher oder mathematischer Notwendigkeit oder mit einer Sicherheit ausschließt, wie sie die Naturwissenschaft etwa bei einem Ausschluß auf Grund der Blutgruppenbestimmung oder allgemein dort anerkennt, wo eine feste kausale Kette keine andere Denkmöglichkeit zuläßt und die Empirie ausnahmslos den Naturgesetzen entspricht», sondern ein «für das praktische Leben brauchbarer Grad von Gewißheit», wobei ausdrücklich darauf hingewiesen wird, daß sich die Aussage des a. e. Gutachtens ja nur im Rahmen von «mehr oder minder großen Wahrscheinlichkeiten» halten kann und der Richter hier nicht «von der schablonenhaften Vorstellung eines mathematisch bestimmten Wahrscheinlichkeitsgrades» ausgehen darf[1]. Es bewegt sich dies also auf einer Basis, welcher in der neueren Terminologie der Genetik der Begriff *plausibility* entspricht.

Und damit hat die deutsche Judikatur die Grenzen dieses Beweismittels sehr zutreffend gewürdigt. Das a. e. Gutachten hat nur die Möglichkeit, induktiv vorzugehen, seine Teilergebnisse des Ähnlichkeitsvergleiches nach Beurteilung der jeweiligen genetischen und sonstigen Umstände (ggf. auch aller genetisch denkbaren Erklärungen für Abweichungen von bekannten Regeln) zu einer Kette von Indizien zusammenzufügen und daraus logisch zu folgern, ob im konkreten Fall nach Abwägung aller Teilresultate die Möglichkeit einer anderen als der schließlich gefundenen Annahme als so gering angesehen werden müßte, daß dies bei den Anforderungen, die das praktische Leben üblicherweise an den Begriff der Gewißheit stellt, nicht mehr in Betracht gezogen werden könnte.

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[1] Urteil vom 14. 7. 1952. Veröffentlicht in der Juristenzeitung, 1952, Nr. 20, S. 628 bis 629.

Dadurch ist auch verständlich, daß eine solche Entscheidung nie frei vom subjektiven Ermessen des Sachverständigen sein kann (wie ja bei jedem Gutachten, welches nicht etwa nur völlig objektivierte Befunde unter stets zwingenden ausnahmefreien Regeln zu beurteilen hat) und daß nach allgemeinen Voraussetzungen der Humangenetik (nämlich der sehr starken Variabilität des Menschen in genotypischer und phänotypischer Hinsicht) von vornherein schon mit einer Variabilität der Ergebnisse und damit auch ihrer Beweiskraft bei dieser Art der Expertise gerechnet werden muß.

In diesem Rahmen hat sich aber in der langjährigen Praxis der zahlreichen Gutachter in Deutschland und Österreich eine Übereinstimmung der Auffassungen herausgebildet, wonach auch bei Fehlen eines serologischen Ergebnisses, dem infolge biostatistischer Sicherung nach dem Usus fori bereits singulär volle Beweiskraft zukommt, für den *Vaterschaftsausschluß* ein praktisch ausreichender Grad von Gewißheit (synonym mit dem in einer früheren Entscheidung des Deutschen Reichsgerichtes aufgestellten Begriff der «an Sicherheit grenzenden Wahrscheinlichkeit») begründet sein kann, wenn Umstände vorliegen wie:

1. Auftreten von dominanten Erbmerkmalen beim Kind, wenn weder die Mutter noch der betreffende Mann diese Merkmale besitzen. Es gilt dies für alle normalen oder pathologischen Eigenschaften mit theoretisch gesichertem, wenn auch nicht regelmäßig dominantem Erbgang (die ausnahmslos regelmäßigen Dominanz-Rezessivitäts- und Kombinanzverhältnisse bei den Bluttypensystemen bleiben hier ja außer Betracht), ferner für alle Eigenschaften mit besonderen erfahrungsgemäßen Erbregeln, aber noch nicht gesicherten oder eindeutigen Genhypothesen (z. B. Hautfarbe, Augenfarbe, Haarfarbe, Haarform, bestimmte quantitative Kriterien des Hautleistensystems).

2. Abweichung des Kindes von der Mutter und von dem betreffenden Mann in einer großen Anzahl vererblicher Merkmale, wenn sich diese auf zahlreiche Körperregionen verteilen, oder in Komplexen erbbedingter Einzelheiten, welche ganze anatomisch abgrenzbare Gebiete besonders charakterisieren.

Nicht weniger praktische Bedeutung hat aber auch die *positive Feststellung der Vaterschaft* gewonnen, bei der geprüft wird, ob sich ein analoger Grad der Gewißheit für die Annahme ergibt, daß das Kind den väterlichen Anteil seiner Anlagen nicht von einem anderen Mann als dem in Frage stehenden erhalten haben konnte, wodurch sich auch zwingend ein gleicher Grad der Gewißheit für den Ausschluß der Vaterschaft anderer, unter Umständen auch bestimmter in die Untersuchung einbezogener Männer ergeben muß, selbst wenn allein auf Grund der Konstellation der Befunde des

Kindes, der Mutter und dieser männlichen Vergleichspersonen noch nicht der Ausschluß der Vaterschaft der letzteren Männer erwiesen werden könnte. Auch das Prinzip dieses sogenannten indirekten Ausschlusses hat in der Deutschen Judikatur durchaus Anerkennung gefunden, zumal ein solches Ergebnis unter bestimmter prozessualer Beweislage eine richterliche Entscheidung ermöglichen kann, die aus rechtlichen Gründen ohne diesen Beweis nicht getroffen werden könnte.

Für den positiven Vaterschaftsnachweis sind nun nach herrschender Auffassung folgende Bedingungen von besonderer Bedeutung:

1. Fehlen erheblicher Abweichungen des Kindes von Mutter und Mann (in gleicher Richtung), und zwar sowohl etwa kleiner Differenzen in zahlreichen Einzelheiten als auch starker Unterschiede in bestimmten Einzelmerkmalen oder regionären Merkmalskomplexen oder überhaupt in Eigenschaften, welche nach dem Erkenntnisstand der Genetik beim Kind die Manifestation von Anlagen erweisen könnten, deren Vorhandensein bei der Mutter wie auch bei dem betreffenden Mann auszuschließen oder als unwahrscheinlich anzusehen wäre.

2. Gleichartige Befunde bei Kind und Mann in den meisten anlagebedingten Merkmalen, in denen das Kind von der Mutter so stark abweicht, daß die betreffenden Differenzen von Kind und Mutter auf Unterschiede zwischen den bei diesen Personen manifestierten Anlagen zurückgeführt werden müßten oder eine solche Annahme nach Forschung und Erfahrung zumindest wahrscheinlich wäre.

3. Vorhandensein von seltenen Körpermerkmalen, die sich in direkter Folge vererben können oder sogar regelmäßig dominanten Erbgang haben, oder von Komplexen erbbedingter körperlicher Einzelheiten, welche ganze anatomisch abgegrenzte Regionen besonders charakterisieren, und zwar unter der in Ziffer 2 angegebenen Konstellation von Kind, Mutter und Mann. Ein ebenso beweiskräftiges Moment kann auch dann vorliegen, wenn die Ähnlichkeit von Kind und Mann sich auf einen viel größeren Teil der gesamten Befunde erstreckt als die Ähnlichkeit von Kind und Mutter, obwohl es sich nicht im einzelnen jeweils um seltene Erbmerkmale handelt.

Damit besitzt also die Praxis Richtlinien, welche die großen Schwierigkeiten der gutachtlichen Entscheidung im Einzelfall wohl erleichtern, aber noch nicht beseitigen können. Es besteht kein Zweifel, daß der Beweis, den wir nach dem derzeitigen Stand der Erkenntnis mit diesem Verfahren zu liefern vermögen, gegenüber den Anfängen der Humangenetik sicher einen gewaltigen Fortschritt bedeutet. Wir sehen auch, daß wir bei sorgfältiger, vorsichtiger und verantwortungsbewußter Expertise dem Rechtsleben Dienste leisten, die in ihrem Umfang (schon nach der jähr-

lichen Zahl solcher Gutachten) sehr groß sind und heute in der deutschen Rechtspflege bereits als durchaus unentbehrlich betrachtet werden. Aber wir sind uns auch darüber klar, daß das Verfahren des anthropologisch-erbbiologischen Gutachtens nach seinem jetzigen Stand im Aspekt exakt genetischen Denkens nur ein Hilfsmittel sein kann, bis uns die weitere Forschung bessere und auch praktisch einfachere Möglichkeiten bietet.

Bauermeister, W.: Acta genet. *6*, 596–598, 1956/57

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BIOMETRISCHE METHODEN DER VATERSCHAFTSDIAGNOSE

Von W. BAUERMEISTER

Von den verschiedenen biometrischen Methoden, die zur Klärung strittiger Vaterschaftsfälle entwickelt wurden, sind besonders die *Essen-Möller*-Formel und die Diskriminanzanalyse hervorzuheben. Über die *Essen-Möller*-Formel liegen bereits eine Reihe von Berichten vor, die übereinstimmend gute Erfolge mit dieser Methode mitteilten. Die Diskriminanzanalyse befindet sich noch im Zustand der Entwicklung und ist bisher nur von *Bauer* und *Baitsch* herangezogen worden.

Da sich diese Ansätze bei *Bauer* und *Baitsch* nur auf das Verhältnis Kind-Vater bezogen, und auch das Kind-Vater-Verhältnis nicht direkt festgestellt ist, wurde mit einem anderen Ansatz in einem Modell von 200 echten Vater-Mutter-Kind-Terzetten und 200 zufällig kombinierten Terzetten die Diskriminanzanalyse durchgeführt. Es ist dabei das *Penrose*-Verfahren gewählt worden, um eine möglichst große Zahl von Einzelmerkmalen berücksichtigen zu können. Die *Smith*-Analyse ist gleichfalls durchgeführt, doch bot sie keine wesentlichen Vorteile.

Der Arbeitsaufwand ist, wenn einmal die Diskriminanzfunktion entwickelt ist, jedoch nicht wesentlich größer, so daß auch diese Methode zur Probe stets mitgeführt werden sollte.

Das Ausgangsmaterial umfaßte 1200 bis 3000 sichere Eltern-Kind-Kombinationen sowie zur Bestimmung der Häufigkeit der einzelnen Merk-

male ein wesentlich größeres Untersuchungsgut, um ein sicheres Urteil über die Alters- und Geschlechtsabhängigkeit zu gewinnen. Bei alternativen Merkmalen waren in einer Achtfeldertafel damit sämtliche Kombinationsmöglichkeiten erfaßt. Bei fluktuierender Variabilität wurde mit drei Klassen —, O und + gearbeitet. Die O-Klasse ist dabei definiert als $\bar{x} \pm \frac{S}{2}$ umfaßt also bei normaler Verteilung knapp die Hälfte des Kollektivs. Hier war bereits eine 27-Felder-Tafel nötig und damit in unserem Material die Grenze der Merkmalsdifferenzierbarkeit erreicht. In diesen 8- bzw. 27-Felder-Tafeln wurde unter Berücksichtigung der Mutter bei echten Vätern die Häufigkeit der Konkordanz bzw. Diskordanz zwischen Vater und Kind bestimmt und mit dem aus der Merkmalsverteilung zu erwartenden Häufigkeitswert verglichen. Bezeichnen wir mit E die empirisch bestimmte Häufigkeit und mit F die theoretisch zu erwartende, so ist das Ausgangsmerkmal definiert als E-F; es erwies sich dabei als günstiger, nicht den absoluten Häufigkeitsunterschied herauszuziehen, sondern ihn in Beziehung zu setzen zur zufälligen Konkordanz; so nimmt das Ausgangsmerkmal endgültig den Wert $X = \frac{E-F}{F}$ oder $X = \frac{E}{F} - 1$ an. Überwiegt die Häufigkeit bei echten Vätern, so wird der Wert positiv, im umgekehrten Fall negativ, wird $E = F$, so wird $X = O$. Diese relative Steigerung der zufällig zu erwartenden Konkordanz bei echten Vätern wurde normiert, indem die Werte durch die mittlere quadratische Abweichung geteilt wurden. Für rund 200 phänotypische Merkmale sind die X-Werte bestimmt, von ihnen 49 ausgewählt und aus ihnen Ausdehnungs- und Profilmaß berechnet. Die Diskriminanzfunktion ließ sich bestimmen als $X = 2{,}24\,a + p$. Das Modell zeigt, daß von 200 falschen Vätern nur 11 in den Bereich der echten Väter, umgekehrt, von 200 echten Vätern 33 in den Bereich der falschen hineinfallen. Allerdings überschreiten die echten Väter den Grenzwert weniger weit als die falschen. Die Überschneidungszone falscher und echter Väter umfaßt rund 55 %, während der Rest eindeutig zu diagnostizieren ist. Bei einer statistischen Sicherheit von 99 % steigt der Anteil der diagnostizierbaren Fälle auf 57 %, bei einer Sicherheit von 95 % auf 80 %. Eine weitere Verbesserung der Trennschärfe läßt sich erreichen, wenn bereits bei der Konstruktion des Ausgangsmerkmals das Geschlecht des Kindes mitberücksichtigt wird, wie sich aus den Unterschieden der Häufigkeit und des Grades der Überschneidung bei Söhnen und Töchtern ergibt, ferner durch eine feinere Aufgliederung der Merkmale sowie durch die Heranziehung weiterer Merkmale. Für das Modell sind nur Merkmale des Blutsystems, der Pigmentierung, des Papillarsystems sowie anthropometrische Befunde herangezogen. Auf die

Verwendung physiognomischer Merkmale ist in dem Modell verzichtet, um das Ergebnis des polysymptomatischen Ähnlichkeitsvergleiches, das sich ausschließlich auf physiognomische Merkmale stützt, mit einer unabhängigen Methode überprüfen zu können. Die Aufgliederung der Merkmale setzt eine sehr große Zahl von Einzelbeobachtungen voraus. Ein weiterer Ausbau der Diskriminanzanalyse in dieser Richtung ist jedoch als erfolgversprechend zu bezeichnen.

Nach der Festlegung der Diskriminanzfunktion bei tatsächlichen und falschen Vätern wurde ein Vergleich der Ergebnisse der Diskriminanzanalyse, der *Essen-Möller*-Formel und des polysymptomatischen Ähnlichkeitsvergleiches an strittigen Vaterschaftsfällen durchgeführt. Sowohl der *Essen-Möller*-Wert wie auch der X-Wert der Diskriminanzanalyse zeigten dabei eine starke positive Korrelation zum Ergebnis der polysymptomatischen Ähnlichkeitsdiagnose. Für die *Essen-Möller*-Formel konnte 1955 auf der Biometrikertagung in Bad Nauheim bereits gezeigt werden, daß zwar bei einem positiven physiognomischen Urteil nur recht selten niedrige *Essen-Möller*-Werte zu finden waren, daß sich aber bei einem negativen physiognomischen Urteil häufiger Werte fanden, die in den von *Essen-Möller* als positiv zu bezeichneten Bereich hineinfielen. Der Grund dürfte darin liegen, daß die Korrelationen, die alle verwandten Merkmale untereinander besitzen, nicht völlig übersehbar und ausschaltbar sind. Diskrepanzen zwischen *Essen-Möller*-Formel und Ähnlichkeitsvergleich ergaben sich bei positivem physiognomischen Urteil in rund 2 %, bei negativem in 10 % der Fälle. Die Außenfelder sind dabei allerdings nicht besetzt. Bei der Diskriminanzanalyse sind diese Diskrepanzen bedeutend seltener. Hervorzuheben ist die Überprüfung einer Gruppe, bei der nach dem physiognomischen Ähnlichkeitsvergleich durch die Bestimmung der Rh-Untergruppen ein Ausschluß möglich war. Während bei der Diskriminanzanalyse in keinem der Fälle die Überschneidungszone in positiver Richtung überschritten wurde, fanden sich hier in 2,5 % der Fälle positive *Essen-Möller*-Werte. Abschließend kann daher bei einem Vergleich der beiden biometrischen Methoden gesagt werden, daß bei beiden das negative Urteil sicherer ist als das positive, und daß die Diskriminanzanalyse auch bei den positiven Urteilen genauer arbeitet als die *Essen-Möller*-Formel.

Discussion

F. Keiter (Hamburg): Es darf nicht unbeachtet bleiben, daß die Anwendung von Wahrscheinlichkeitskombinationen auf Blutgruppenbeweise eine Signifikanzprüfung nötig macht. Es müssen immer «kritische Werte» gebildet werden, d. h. Häufigkeiten bei bestehender und nichtbestehender Vaterschaft verglichen werden. Die Anzahl der möglichen Kombinationen ist begrenzt, ihr Wahrscheinlichkeitswert sehr inhomogen.

Wichmann, D.: Acta genet. *6*, 599–602, 1956/57

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DIE VERWENDUNG DER FUSSOHLEN-BEMUSTERUNG IM RAHMEN DER VATERSCHAFTSBEGUTACHTUNG

Von D. WICHMANN

Der polysymptomatische erbbiologische Vaterschaftsnachweis ist an verschiedene Voraussetzungen gebunden.

1. Nachweis der Erblichkeit der Merkmale,
2. Gute Definierbarkeit,
3. Möglichst unabhängig von Alterswandel und Geschlecht,
4. Keine Korrelation mit anderen verwendeten Merkmalen.

Zu 1: Es ist nicht erforderlich, daß ein einfacher, d. h. von einem einzigen Genpaar abhängiger Erbgang vorliegt. Polymer bedingte Merkmale sind ebenfalls geeignet, nur sind sie in ihrer Information etwas eingeschränkt (Fehlen des «Ausschlusses»).

Zu 2: Der Frage der Definitionsqualität der Merkmale wurde bisher zu wenig Beachtung geschenkt. Schwer bestimmbare Merkmale sind oft der Grund für divergierende Urteile (sowohl beim Gutachten wie in der Literatur).

Zu 3: Soweit Urteile auf Grund eines größeren Familienmaterials (Behandlung des Gutachtens als Stichprobe aus diesem) erfolgen und hierbei statistische Verfahren angewandt werden, sind Alters- und Geschlechtsunterschiede bereits berücksichtigt.

Zu 4: Gegen die Prämisse der Unabhängigkeit der kombinierten Merkmale wird am häufigsten verstoßen, obschon *Weinberg* [6] vor über 25 Jahren auf dieses Problem bei der Zwillingsdiagnose aufmerksam machte, indem er Berücksichtigung der 24 menschlichen Koppelungsgruppen forderte. Zu diesem Punkt liegen auch relativ wenig Untersuchungen vor.

Der distale Teil der menschlichen Fußsohle trägt 5 Ballen: Thenar,

Hypothenar und 3 Mittelfußballen (= Felder I–III), die als Entstehungszentren der Papillarmuster während der fötalen Entwicklung zu betrachten sind. Wie auf der Handfläche dürften drei Faltensysteme von Bedeutung sein: 1. die Arealfaltung (von den Zehenwurzeln in proximaler Richtung tendierend), 2. die Seitenfaltung (zwischen den Ballen) und 3. die Furchenfaltung (von der Fußmitte distal tendierend).

Die Erblichkeit der Fußsohlenmuster ist erwiesen durch Zwillingsunteruntersuchungen (*Geipel* [4], *Wichmann* [8]) und Familienuntersuchungen (*Wichmann* [9]). Nach den serologischen Merkmalen dürften sie wohl zu den am besten definierbaren Formmerkmalen gehören, wenn keine überfeinerte Klassifizierung vorgenommen wird. Auch bestehen keine grundlegenden Alters- und Geschlechtsunterschiede. Durch die Faltungssysteme bedingt, liegen aber enge Korrelationen zwischen allen 5 Ballen bezüglich ihrer Muster vor, wobei die Arealfaltung (Proximal-, Tibialschleifen und Wirbel), die Furchenfaltung (Distalschleifen) und die Seitenfaltung (offene Felder) deutlich erkennbar sind. Nur die Muster von Thenar und Hypothenar sind von einander unabhängig (*Wichmann*). Offenbar ist also die Bemusterung der menschlichen Fußsohle durch mehrere polyphän wirkende Genpaare (eventuell Allelenreihen) bedingt. Monomere Erbgänge ließen sich nicht nachweisen, so daß Vaterschaftsausschlüsse wie bei den Blutgruppen durch die Fußsohlenbemusterung allein nicht möglich sind.

Diese Merkmalskorrelationen widersprechen zunächst der vierten Prämisse. Ihre Nichtberücksichtigung würde falsche übermäßig zu den Extremen tendierende Resultate ergeben, es sei denn, man wolle sich auf Thenar- und Hypothenarmuster beschränken. Da die Korrelationen jedoch nicht absolut sind, würde man durch völligen Verzicht Informationen verlieren. Unsere Aufgabe ist es, eine Methode zu finden, die korrekte Ergebnisse liefert.

Da bei der Zwillingsdiagnose prinzipiell die gleichen Prämissen vorliegen wie bei der Vaterschaftsbegutachtung, wurde zunächst an einer Zwillingsserie (58 EZ- und 44 ZZ-Paare) versucht, eine geeignete Methode zu entwickeln. Beim Versuch, Merkmale «Areal-», «Seiten-» und «Furchenfaltung» zu bilden, zeigten sich zwar echte Unterschiede zwischen den EZ und ZZ, aber gleichzeitig auch eine relativ geringe Variabilität dieser Merkmale. Nun unternahmen es *Cummins* und *Midlo* [1] vor 14 Jahren, die Fingerbeerenmuster in einer Bewertungsskala zu klassifizieren, ein ähnliches Verfahren wandte später auch *Keiter* [5] an. Bei unserer Klassifizierung der Fußsohlenmuster wurde «offenes Feld» mit 1, Schleife (gleich welcher Richtung) mit 3, Wirbel mit 5, doppelzentrische Wirbel mit 6, Übergangsmuster mit 2 (Spur) bzw. mit 4 (Muschelschleife, Zentraltasche)

benotet. Die zu addierenden Werte ergeben das neue Merkmal «Mustersumme». Der theoretische Schwankungsbereich beträgt 10 bis 60, der tatsächliche 12 bis 36. Der Paarlingsunterschied war bei den EZ ($M = 1{,}60 \pm 0{,}19$) wesentlich geringer als bei den ZZ ($M = 4{,}32 \pm 0{,}44$).

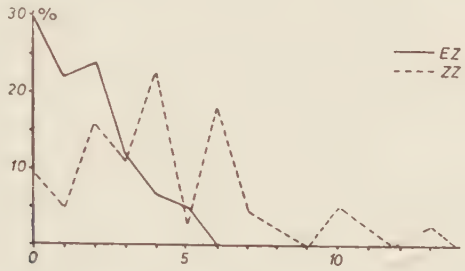

Abb. 1. Das Merkmal «Mustersumme» bei Zwillingen

Um in dem nun zu bearbeitenden Familienmaterial alle Möglichkeiten der illegitimen Abstammung oder der Fehldiagnose des Gutachters auszuschalten, wurde der Versuch nur auf den Mutter-Kind-Vergleich abgestellt, da der Paarvergleich auch im Vaterschaftsgutachten möglich ist. Hierbei ergab sich, daß auch bei bestehender Verwandtschaft nicht unerhebliche Differenzen in den Mustersummen möglich sind, im Mittel betrug der Kind-Mutter-Unterschied $4{,}68 \pm 0{,}16$ und entspricht damit dem Unterschied zwischen ZZ. Für einen Blindversuch wurden den Kindern nach einem bestimmten Zufallsschema «falsche Mütter» zugeordnet. Die hierbei entstehende Differenz zwischen Kind und «falscher Mutter» belief sich im Durchschnitt auf $8.24 \pm 0{,}20$. Auch war die Standardabweichung der Differenzen zwischen Kindern und «falschen Müttern» ($\sigma = 4{,}62 \pm 0{,}14$) höher als bei Kindern und wahren Müttern ($\sigma = 3{,}58 \pm 0{,}11$).

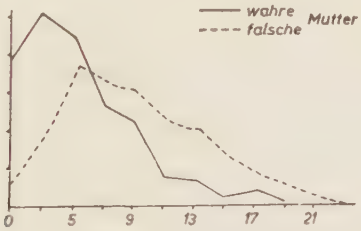

Abb. 2. Das Merkmal «Mustersumme» bei Kindern und Müttern

Dieses Merkmal kann, soweit nach den obigen Voraussetzungen zulässig, mit weiteren Merkmalen kombiniert werden, etwa in der *Essen-*

Möller-Formel [2], dem χ^2-Test [10] oder der Diskriminanzanalyse. Für das *Essen-Möller*-Verfahren seien noch auf Grund des Paarvergleichs Mutter-Kind die «kritischen Werte» (kW) gebracht. Je nach Höhe der «Mustersumme» hat man Kind wie Mutter in eine der drei Klassen «niedrig» = n (x–18), «mittel» = m (19–23) oder «hoch» = h (24–x) einzugruppieren. Jede dieser drei Klassen umfaßt ungefähr ein Drittel des Kollektivs. Zwischen Müttern und Kindern besteht kein grundlegender Unterschied. Y bedeutet die Häufigkeit des kindlichen Merkmals in der mütterlichen Population, X die Häufigkeit unter wahren Müttern in unserem Material.

Es dürften kaum Bedenken bestehen, diese Werte auch für die praktische Vaterschaftsdiagnose zu verwenden. Bei Benutzung der Formel von *Essen-Möller* und *Quensel* [3] erhöhen sich in Mehr-Mann-Fällen die Pl.-Werte auf ungefähr 65 %:35 %. Das Merkmal «Mustersumme» ist daher für die Vaterschaftsdiagnose grundsätzlich geeignet, wegen der Überschneidungen dürfte es allein nicht ausreichen.

Kd.	Mu.	Y : X	kW	Pl.%
	n	34,6 : 46,1	0,75	57
n	m	33,8 : 33,2	1,02	49
	h	31,6 : 20,5	1,54	39
	n	34,6 : 33,2	1,07	48
m	m	33,8 : 36,4	0,93	52
	h	31,6 : 30,4	1,04	49
	n	34,6 : 27,2	1,31	43
h	m	33,8 : 30,6	1,10	48
	h	31,6 : 42,2	0,75	57

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Jonsson, B.: Acta genet. *6*, 603–606, 1956/57

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BLOOD GROUPS AND PATERNITY PROBLEMS

By B. JONSSON

Landsteiner's discovery of the human blood group system, now named the ABO system [1901], gave rise to a long series of the theoretically and practically most important conquests in human genetics. *Landsteiner*'s discovery can be said to be a twin to the rediscovery of *Mendel*'s laws.

The 2-gene theory of *von Dungern* and *Hirzfeld* as to the inheritance of the ABO system [1910] was soon superseded by *Bernstein*'s 3-gene theory [1924] with the A, B and O genes as allelomorphs. Almost simultaneously *Furuhata* presented an essentially equivalent theory.

The ABO system thus gave us, as far as I know, the first proved example of multiple allely in human genetics. Later the blood group research should give a phantastic collection of examples, of nearly all known genetical phenomena, with an exception so far of sex-linkage.

The knowledge of the inheritance laws for the blood group systems very soon received forensic application to problems of parentage, especially for exclusion of paternity.

In the Roman countries influenced by the Code Napoléon the interest was of course minimal, but in the Anglo-Saxon countries too the progress in this sphere was slow. The interest in Germany and the Scandinavian countries, however, was all the greater, in spite of laws, which at least in the beginning were rather unfavourable for forensic use of genetical proofs. Supposing a man had had coition with the child's mother during the possible time of conception, the Court had to confirm his paternity if it was not evidently impossible for him to be the child's father. Protracted and in part highly philosophical struggles about the concept "offenbar unmöglich" were fought, but have now, with exception of a slight after-effect, calmed down.

The work of legislation in these respects during the last decade shows in Sweden as well as in the rest of Scandinavia a very good example

of reciprocally fruitful co-operation between juridical and blood group genetical experts.

By routine, we at the State Laboratory of Forensic Chemistry in Sweden, carry out all investigations in paternity cases using the A_1A_2BO, the MN and the P systems as well as the results with the four principal anti-Rh sera: anti-C, anti-c, anti-D and anti-E. These systems, which have won complete approval from our courts, give with the Swedish gene frequencies a theoretical chance for direct paternity exclusion of about 52%.

The evolution of the blood group science, especially with respect to the subgroups of the Rh system, has, however, not only given increased possibilities to direct paternity exclusions, but also considerably increased possibilities of judging the probability or improbability of paternity, respectively.

Parallel with this evolution, a more biological way of looking at the matter arose among our law-makers. In intimate team-work with genetical experts they prepared new Swedish laws of paternity which came into force on the first of January 1950. It was, inter alia, prescribed that a man, who had had coition with the child's mother during the possible time of conception, should be appointed the child's father, if it was not improbable that the child had been conceived through that coition. In this way, judging of the paternity probability is of great legal importance and we nowadays in our paternity cases always give a verdict upon the so-called relative probability of paternity in comparison with a man selected at random from the population.

A project now presented for new Swedish laws of inheritance can, if approved, give far more importance to these calculations of probability. It is, inter alia, prospected for an extramatrimonial child to have complete share of inheritance from his father. If two or more men are suspected for the paternity, the one whose paternity is most probable shall be appointed. If there is no greater probability for one of them, they all shall be released from the paternity. Analogous law-prospects are worked at in all the Scandinavian countries.

The highly positive attitude of our law-makers to the results of the blood group investigations in paternity cases is very satisfactory but has led to a tendency to exaggerate the value of the apparently exact mathematical figures of probability. Our most actual mission, at least in Sweden, is in an appreciable degree not to struggle for the use of the probability calculations but to struggle against the misuse of them. The legal position of the blood-group statistical proofs in Sweden is thus rather strong, but there are not yet any clearly conclusive precedents by the King's Court.

The reason is the unusualness of carrying paternity cases to the court of highest instance.

In our Swedish laboratory material of about 1,500 complete paternity cases per year the found frequency of exclusions is about 40 % of the theoretical chance of exclusion, which means actual promiscuity in the great majority of the cases. The material to about seven-eights concerns extramatrimonial children and to about one-eighth questionably legitimate birth. The blood group investigations are to a great extent (about 50 %) carried out before the opening of legal proceedings.

In a little more than 300 of these 1,500 paternity cases there are direct exclusions of paternity, in about 500 cases there are relative probabilities of paternity higher than 75 %, and in about 25 cases there are relative probabilities of paternity smaller than 25 %. In about 20 of the 25 cases last mentioned the relative probabilities of paternity are smaller than 3 %. Cases of the latest type are often but not quite correctly called "statistical exclusions".

For our probability calculations we use the A_1A_2BO system, the MN system and the results with the four principal anti-Rh sera, but only to a smaller extent the P system, which is too complex for routine probability use.

The calculations of probability thus give a good help for the judging of paternity cases, but it clearly is of extreme importance to point out to the courts and lawyers that the blood group statistical probability is only one probability among many others in the case and that the other perhaps not so seductively mathematically demonstrable probabilities have to be considered. Among such other probabilities I can especially name the results of anthropological investigations and the date of coition in the possible time of conception, but numerous other facts can be of importance too. Only in this way one can prevent a misuse of the blood group statistical method.

One must never forget the possibility of an influence from not only geographical but also social and even family isolates on the value of the calculations of probability and of course not the rare possibility of mosaicism, suppressing genes and so on, the latter things of greater importance however by the paternity exclusions. Great caution is needed by paternity exclusions based on the finding of extremely rare genes by the children.

In such cases where only one man is pointed out as the possible father, one ought to be particularly cautious with the use of the probabilities, in cases with two or more possible fathers one can be a little more liberal with the judging. The cases with two or more possible fathers are especially

convenient for comparison of probabilities, but perhaps also especially tempting to misuse too small differencies of probabilities.

The probabilities and improbabilities won through blood group investigations can in favourable cases be of an extreme height.

The use of other blood group systems than the above mentioned, Kell, Duffy, S, Lewis and so on, can in special cases be of great importance for exclusions and judging of probability, but the antisera needed are not yet always available. The evolution of the blood group science is of course very rapid and great new possibilities can be expected. In all the legitimate optimism we must, however, try to stand with both our feet on the solid ground.

Hässig, A., S. Rosin, A. Schmid et *B. Wuilleret:* Acta genet. *6*, 606, 1956/57

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LA VALEUR MÉDICO-LÉGALE DES FACTEURS SANGUINS A_1, A_2, K, Fy^a ET P

Par A. HÄSSIG, S. ROSIN, A. SCHMID et B. WUILLERET

La première partie de cette conférence paraîtra sous le titre «Über die Verwertbarkeit der Blutfaktoren A_1, A_2, K, Fy^a und P bei der Klärung von strittigen Abstammungsfragen» par *B. Wuilleret, S. Rosin* et *A. Hässig*, dans la «Schweizerische Medizinische Wochenschrift» 1956. La seconde partie sera publiée par *A. Schmid* sous le titre «Über Intermediärformen der A-Untergruppen» dans le journal «Blut» 1957.

Nijenhuis, L. E.: Acta genet. 6, 607–611, 1956.57

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PROBABILITY OF PATERNITY IN CASES WHERE EXCLUSION BY BLOOD GROUP TEST IS NOT POSSIBLE

By L. E. NIJENHUIS

Exclusion of disputed paternity by means of blood group tests is based on reflections of probability. Errors in blood grouping or blood group mutations can never be excluded with certainty. However these possibilities are very unlikely. In fact exclusion of paternity means therefore that paternity is to be considered most unlikely. So, why should we not give equal thought to the probability of paternity calculated on the basis of the results of the blood group tests in cases where exclusion is not possible?

It is a usual procedure to calculate the percentage of men in a certain population that cannot be excluded from paternity with a given mother-child combination. If this percentage is very small, it is obvious to consider paternity of a non-excluded man as being very likely. It seems to me a more reliable method to calculate the probability that the given child might be the result from the combination mother–alleged father.

This method will be demonstrated here by means of an imaginary example of two different men, who neither can be excluded from paternity. The calculation of the chance of exclusion would give for both of them equal probability of paternity. It is, however, the intention to demonstrate that paternity of the first man is very unlikely and paternity of the second man is highly probable.

Table 1 gives the blood group combinations of mother, child and the two men. Under each blood group system of the men a figure is given representing the rate of probability that the man in question, in combination with the mother, might have produced the blood groups found in the child. These probabilities are also mentioned for a random man, as well as the

Table 1.

Mother	O	MNS	CcDee	K—	Fy (a+)	P+	Lu (a—)
Child	A_2	MMss	ccDEe	K—	Fy (a+)	P—	Lu (a—)
Man 1	A_1	MNS	ccddEe	K+	Fy (a—)	P+	Lu (a+)
Probability of the child concerned	0.042	0.013	0.016	0.487	0.625	0.167	0.49
Man 2	A_2	MMss	ccDEe	K—	Fy (a+)	P—	Lu (a—)
Probability of the child concerned	0.525	0.500	0.248	1.000	0.860	0.50	1.000
Random man							
Probability of the child concerned	0.07	0.14	0.071	0.95	0.775	0.25	0.97
Chance of exclusion . .	0.5445	0.221	0.717	0.000	0.000	0.000	0.000
Chance of non-exclusion	0.4555	0.779	0.283	1.000	1.000	1.000	1.000

Table 2

		Genotype	*Gene frequencies*
Mother	O	OO	$p_1 = 0.21$
Child	A_2	A_2O	$p_2 = 0.07$
			$q = 0.06$
			$r = 0.06$

Probability of a child with group A_2

Man 1 (A_1):
- → A_1A_1 impossible
- → A_1A_2 $0.2 \times \frac{A_1A_2}{A_1O + A_1A_1 + A_1A_2} = 0.5 \times \frac{2\,p_1p_2}{2\,p_1r + p_1^2 + 2\,p_1p_2} = 0.042$
- → A_1O impossible

Man 2 (A_2):
- → A_2O $0.5 \times \frac{A_2O}{A_2O + A_2A_2} = 0.5 \times \frac{2\,p_2r}{2\,p_2r + p_2^2}$
- → A_2A_2 $1.0 \times \frac{A_2A_2}{A_2O + A_2A_2} = 1.0 \times \frac{p_2^2}{2\,p_2r + p_2^2}$

} 0.525

Random man must have gene A_2 $1.0 \times$ gene-frequency A_2 0.07

Excludable: groups O, B and A_1B 0.5445

Not excludable: groups A_1, A_2 and A_2B 0.4555

chance of exclusion and non-exclusion of a random man. The method to calculate these probabilities will be demonstrated by means of the calculations for the ABO and Rh systems.

Table 3

Genotypes	*Probability of genotype*	*Gene frequencies*
Mother CcDee → CDe/cde	$\frac{2 \times R_1 \times r}{2 \times R_1 \times r + 2(R_1 + R') \times R_0} = 0.936$	R_1 = CDe = 0.41 R_2 = cDE = 0.14 r = cde = 0.39 R_0 = cDe = 0.026 R′ = Cde = 0.010 R″ = cdE = 0.012
Mother CcDee → CDe/cDe, Cde/cDe	$\frac{2 (R_1 + R') \times R_0}{2 \times R_1 \times r + 2(R_1 + R') \times R_0} = 0.064$	
Child ccDee → cDE/cde, cDE/cDe, cdE/cDe		

		Mother	*Probability of a child ccDEe*	
Man 1 ccddEe	cdE/cde	CDe/cde	impossible	*0.016*
		CDe/cDe, Cde/cDe	0.5 × 0.5 × 0.064	
Man 2 ccDEe	cDE/cde, cDE/cDe	CDe/cde	$0.5 \times 0.5 \times \frac{2 R_2(r + R_0)}{2 R_2(r + R_0) + 2 R'' R_0}$	*0.248*
		CDe/cDe, Cde/cDe		
	cdE/cDe	CDe/cde	impossible	
		CDe/cDe, Cde/cDe	$0.5 \times 0.5 \times 0.064 \times \frac{2 R'' \times R_0}{2 R_2(r + R_0) + 2 R'' R_0}$	
Random man	*must have* cDE	CDe/cDe, Cde/cDe, CDe/cde	0.5 × R_2	*0.071*
	cdE	CDe/cde	impossible	
		CDe/cDe, Cde/cDe	0.5 × 0.064 × R″	

Excludable: all E-negatives $(1-R_2-R'')^2 = 0.717$
not excludable 1–0.717 = *0.283*

As to the first man, three different genotypes are possible; only one of these A_1A_2 could have produced the child with blood group A_2. The

probability that an individual with blood group A_1 has the genotype A_1A_2 is expressed in the following formula:

$$\frac{A_1A_2}{A_1O + A_1A_1 + A_1A_2} \qquad \frac{2\,p_1p_2}{2\,p_1r + p_1^2 + 2\,p_1p_2}$$

The chance that the child inherits the factor A_2 and not the factor A_1 is half of this probability. It has been established that the second man carries the factor A_2. Here we have to consider the probabilities of both genotypes, A_2O and A_2A_2, represented respectively by the formulas:

$$\frac{2\,p_2r}{2\,p_2r + p_2^2} \text{ and } \frac{p_2^2}{2\,p_2r + p_2^2}$$

The chance that the child received the factor A_2 from a random man equals the frequency of the gene A_2.

The calculation for the Rh system is more complicated, as here the mother too can have different genotypes. The probabilities of these genotypes are given in table 3.

The first man can only be the father of a child with the Rh genotype ccDEe, if the mother has the chromosome cDe.

For the second man there are two possibilities: the chromosome cDE and cdE, the probabilities of which are expressed in the formulas:

$$\frac{2\,R_2(r + R_0)}{2\,R_2(r + R_0) + 2\,(R''R_0)} \text{ and } \frac{2\,R''E_0}{2\,R_2(r + R_0) + 2\,R''R_0}$$

The combined probability for each man, composed of the figures for each blood group system separately, is shown in the following table.

Table 4. Probability of having a child A_2 MMss ccDEe K– Fy(a +)P– Lu(a–)

Man 1 . . .	0.042	× 0.013	× 0.016	× 0.487	× 0.625	× 0.167	× 0.49	= 0.000.00022
Man 2 . . .	0.525	× 0.50	× 0.248	× 1.00	× 0.860	× 0.50	× 1.00	= 0.028
Random man	0.07	× 0.14	× 0.071	× 0.95	× 0.775	× 0.25	× 0.97	= 0.000.124
Chance of non-exclusion for a random man	0.4455	× 0.779	× 0.283	× 1.00	× 1.00	× 1.00	× 1.00	= 0.1

Next table gives the conclusion.

Table 5. Probability of paternity

Starting-point	
The appointed man has 50% chance to be the father	
Case 1 appointed man is man 1	
Probability of man 1 : random man = 0.000.00022 : 0.000.124	= 1 : 518
Case 2 appointed man is man 2	
Probability of man 2 : random man = 0.028 : 0.000124	= 226 : 1
Case 3 2 men's case (man 1 and man 2)	
Probability of man 1 : man 2 = 0.000.00022 : 0.028	= 1 : 127.000

Discussion

D. Wichmann (Bonn): Vor einer Reihe von Jahren veröffentlichte *W. Fischer* Tabellen (Dtsch. Z. gerichtl. Med. *37*, 1943), aus denen die Ausschlußchance für einen falschen Vater entnommen werden kann, wenn sein Genotyp durch Untersuchung seiner nächsten Verwandten festgestellt werden kann. Das deutsche Gesetz über die Zivilprozeßordnung gibt dem Richter die Möglichkeit derartige Untersuchungen anzuordnen, wenn eine gewisse Erfolgsaussicht besteht. Bei der Konstellation Mutter O, Kind A_2, Eventualvater A_1 kann unter Umständen sein Genotyp durch Untersuchung seiner Eltern erschlossen werden. Hat ein Elternteil die Blutgruppe O oder B, so muß der Mann den Genotyp A_1O haben und kann daher nicht der Vater eines A_2-Kindes von einer O-Mutter sein.

K. Henningsen (Copenhagen): Dr. *Nijenhuis*'s paper on a constructed example of a statistical parenthood-improbability can be supplemented with the information that the Institute of Forensic Medicine has used similar computations on difficult cases during the last couple of years, and that the statistical improbability in some cases practically exceeds the certainty of exclusion inside the system in question.

Gürtler, H.: Acta genet. *6*, 612–613, 1956/57

University Institute of Forensic Medicine, Copenhagen, Denmark

GENETIC EVALUATION OF BLOOD-GROUPING IN 5,000 PATERNITY CASES WITH A SPECIAL VIEW TO RELATIVE PROBABILITY OF PATERNITY

By H. GÜRTLER

In a population where the genetic structure with regard to blood-groups sufficiently approaches the result of random mating, blood-group determinations in paternity cases—in addition to exclusions—may yield quantitative evidence for or against alleged paternity. Such evidence may be based on elementary genetic calculations and expressed as an estimate of relative probability of paternity of the men concerned.

In Denmark such calculations have been made by way of experiment in 5000 paternity cases involving 17.122 individuals examined according to the blood-group-system A_1B_2BO-MN (S) Rh (CcDE) and P.

The evidence for or against paternity given by a mother-child-father blood-group-combination is expressed as an index stating the frequency of the mother-child-father combination divided by the product of the mother-child frequency and the fathers phenotype-frequency, all frequencies calculated on basis of the gen-frequencies in the Danish population.

Within each of the used blood-group-systems such indices had been calculated for every possible mother-child-father combination and the results have been tabulated.

For a mother-child-father combination in question the indices from the different systems are multiplied to obtain a joint blood-group index. In a single figure this joint index gives the weight of the blood-group-evidence for or against paternity, the index 1 representing the neutral point.

The joint indices for the men in a case are applied to the calculation of the *relative* blood-group-genetical probability of paternity. If the difference between the relative probabilities of the men concerned are great (e.g. 99 %

against 1 %) the calculation may be useful to the court in deciding the case. This is realised in about 200 of the 5000 cases.

In our material about 25 % of the men are excluded. As our theoretical per cent of exclusion is about 50 % it means that about 50 % of the men are not true fathers. The observed distribution of the indices in our material is found to be according to what may be expected under this presumption.

Our methods works rapidly and easily when the tables once have been made. Its applicability depends primarily on the degree of approximation to random mating in the population. If the parties in a case are related to each other or if some of them are members of an isolate this may necessitate special considerations.

It should be mentioned that in cases where there is significant blood-group-genetical evidence for or against the paternity of some of the men concerned it is always emphasized that other circumstances should be taken into account by the court deciding the case.

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University Institute of Forensic Medicine, Copenhagen, Denmark

FORENSIC IMPLICATIONS OF THE D-- CHROMOSOME

By K. HENNINGSEN

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